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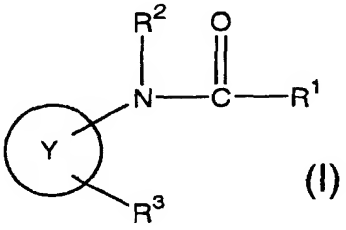
(54) PGD2 RECEPTOR ANTAGONISTIC PHARMACEUTICAL COMPOSITIONS

(57) Compounds of the general formula (I) which are metabolically stable and have an antagonistic activity against PGD_2 receptor:



(I)

wherein Y is bicyclic ring; R^1 is optionally substituted heteroaryl; R^2 is hydrogen, etc.; R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$; R^4 is hydrogen, etc.; X^1 is -O-, etc.

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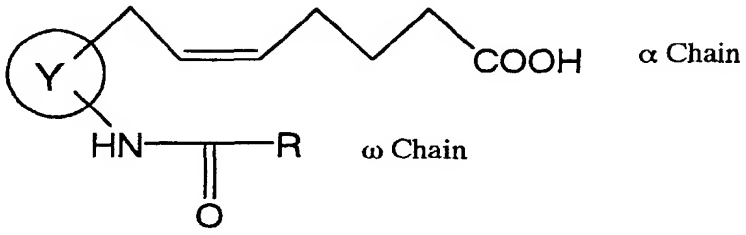
Description

Technical Field

[0001] This invention relates to a bicyclic amide derivative, an antagonist against PGD_2 receptor, and a pharmaceutical composition comprising the same.

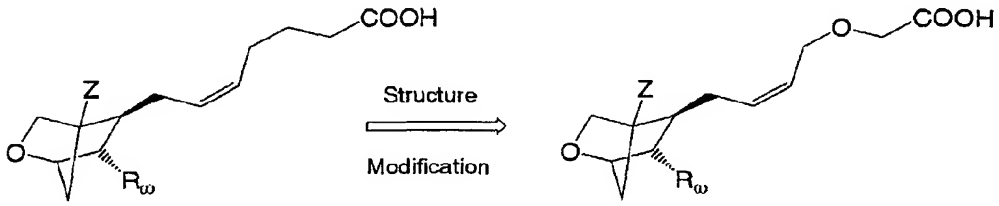
Background Art

[0002] As a pharmaceutical composition comprising an antagonist against PGD_2 receptor, a compound of the formula:



wherein Y is bicyclic ring and R is phenyl etc., was described in WO 97/00853 (International publication date: January 1, 1997).

[0003] On the other hand, it was disclosed that 3-oxa-derivatives were prepared as metabolically stable TXA_2/PGH_2 receptor antagonists in Bioorganic & Medicinal Chemistry Letters, Vol.2, No.9, pp.1069-1072, 1992. The active value of the compound was only described but the metabolic stability has not been described in the literature.



wherein, Z is p-fluorophenyl; Rω is benzenesulfonamino and the like.

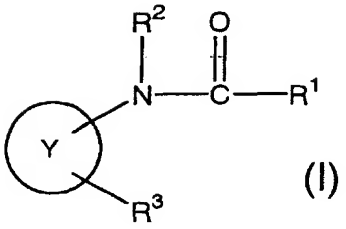
[0004] Furthermore, it was reported in PROSTAGLANDINS, 1986, 31, 95 that ILOPROST, PGI_2 mimetics was stabilized metabolically by converting to the 3-oxa-derivative. But, remaining activity of each compound was only compared under a presence of the metabolic enzyme of a rat and the metabolic stability did not mentioned.

Disclosure of Invention

[0005] The present inventors have carried out the structure modification research on α chain of a pharmaceutical composition comprising an antagonist against PGD_2 receptor described in WO97/00853, found out a metabolically stable antagonist against PGD_2 receptor and have completed the present invention.

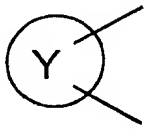
[0006] The present invention provides:

(1) a compound represented by the formula (I):



(I)

wherein



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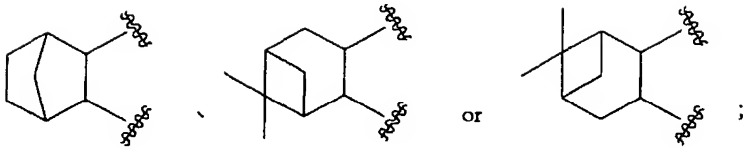
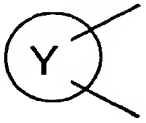


;

R^1 is optionally substituted heteroaryl;
R^2 is hydrogen or alkyl;
R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$;
R^4 is hydrogen or alkyl;
X^1 is -O- or -S-,
a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(2) a compound as described in (1), wherein



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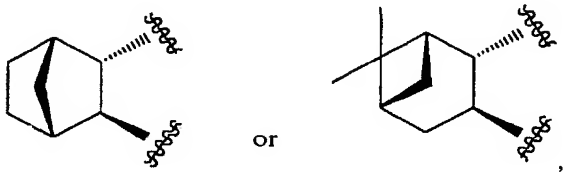


,

a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(3) a compound as described in (1) or (2), wherein R^1 is optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted furyl, optionally substituted benzofuryl, optionally substituted pyrrolyl, optionally substituted thienopyrrolyl or optionally substituted indolyl, a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(4) a compound as described in (1) or (2), wherein R^1 is heteroaryl which may be substituted with a group of the formula: $-Z^1-Z^2$ wherein Z^1 is a bond, -O-,-S-, -NH-, -NH-C(=O)-, -NH-C(=O)-O-, $-NH-SO_2-$, -C(=O)-, -O-C(=O)-, -C(=O)-O-, $-SO_2-$, $-CH_2-O-$, $-CH_2-NH-C(=O)-$, $-CH_2-NH-C(=O)-O-$, $-CH_2-NH-SO_2-$ or $-CH_2-C(=O)-$ and Z^2 is alkyl or optionally substituted amino; carboxy; halogen; hydroxy; or nitro, a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(5) a compound as described in any one of (1) to (4), wherein R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$; R^4 is hydrogen; and X^1 is-O- or -S-, a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(6) a compound as described in (5), wherein R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$ or $-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$; R^4 is hydrogen; and X^1 is -O- or -S-, a prodrug, a pharmaceutically acceptable salt or a solvate thereof,

(7) a pharmaceutical composition containing a compound, a prodrug, a pharmaceutically acceptable salt, or a solvate thereof as described in any one of (1) to (6),

(8) a pharmaceutical composition having an antagonistic activity against PGD_2 receptor as described in (7),

(9) a pharmaceutical composition as described in (7), which is used for the treatment of nasal,

(10) a pharmaceutical composition as described in (7), which is used for the treatment of allergic conjunctivitis,

(11) a pharmaceutical composition as described in (7), which is used for the treatment of allergic rhinitis,

(12) a method for treating nasal blockage, allergic conjunctivitis or allergic rhinitis, which comprises administrating a composition as described in (7), and

(13) use of the compound as described in any one of (1) to (6) for the preparation of a pharmaceutical composition for treating nasal blockage, allergic conjunctivitis or allergic rhinitis.

[0007] The terms used herein is explained below. Each term used herein is defined to have meanings below in either case of a single or a joint use with other terms.

[0008] The term "heteroaryl" includes a 5- to 7-membered aromatic heterocycle containing one or more oxygen atom, sulfur atom and/or nitrogen atom in the ring, or such an aromatic heterocycle as fused with one or more carbocycle or other aromatic heterocycle, which has a bond at any substitutable. Any one of aromatic heterocycle and aromatic carbocycle may have a bond.

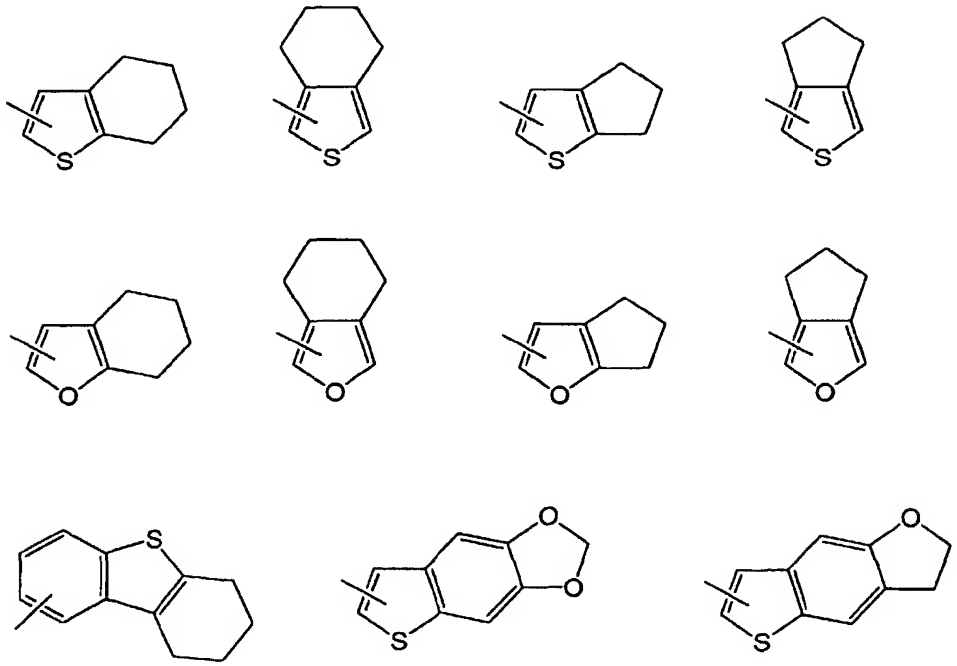
[0009] Examples of "heteroaryl" include pyrrolyl (e.g., 2-pyrrolyl, 3-pyrrolyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrazolyl (e.g., 3-pyrazolyl, 4-pyrazolyl), imidazolyl (e.g., 2-imidazolyl, 4-imidazolyl), pyrimidinyl (e.g., 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), indolyl (e.g., 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), carbazolyl (e.g., 1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), benzimidazolyl (e.g., 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl), indazolyl (e.g., 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), quinolyl (e.g., 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (e.g., 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), furyl (e.g., 2-furyl, 3-furyl), benzofuryl (e.g., 2-benzofuryl, 3-benzofuryl, 4-benzofuryl, 5-benzofuryl, 6-benzofuryl, 7-benzofuryl), thienyl (e.g., 2-thienyl, 3-thienyl), benzothienyl (e.g., benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, benzo[b]thiophen-4-yl, benzo[b]thiophen-5-yl, benzo[b]thiophen-6-yl, benzo[b]thiophen-7-yl), dibenzothienyl (e.g., 2-dibenzothienyl, 3-dibenzothienyl), dibenzofuryl (e.g., 2-dibenzofuryl, 3-dibenzofuryl), naphthothienyl (e.g., naphtho[2,3-b]thiophen-2-yl, naphtho[2,3-b]thiophen-3-yl, naphtho[1.2-b]thiophen-2-yl, naphtho[1.2-b]thiophen-3-yl), oxazolyl (e.g., 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (e.g., 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (e.g., 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), isothiazolyl (e.g., 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl), imidazothiazolyl (e.g., imidazo[2.1-b]thiazol-2-yl, imidazo[2.1-b]thiazol-3-yl), benzoisoxazolyl (e.g., benzo[d]isoxazol-3-yl), benzothiazolyl (e.g., benzo[d]thiazol-2-yl), thienopyrrolyl (e.g., thieno[2,3-b]pyrrole-2-yl, thieno[2,3-b]pyrrole-3-yl, thieno[2,3-b]pyrrole-5-yl, thieno[2,3-c]pyrrole-2-yl, thieno[2,3-c]pyrrole-4-yl, thieno[3,2-b]pyrrole-2-yl, thieno[3,2-b]pyrrole-3-yl, thieno[3,2-b]pyrrole-5-yl), and the like.

[0010] Thienyl, benzothienyl, furyl, benzofuryl, pyrrolyl, are indolyl preferred.

[0011] The term of "aromatic carbocycle or other aromatic heterocycle" which may fuse the above "heteroaryl" includes 5- to 7-membered aromatic cycle which may contains one or more oxygen atom, sulfur atom and/or nitrogen atom in the ring, or such an aromatic ring as fused with one or more other aromatic rings.

[0012] The above "heteroaryl" may be fused 4- to 7-membered cycloalkane or 4- to 7-membered non-aromatic heterocycle. Examples of cycloalkane include cyclobutane, cyclopentane, cyclohexane, and cycloheptane. Examples of non-aromatic heterocycle include pyrrolidine, piperazine, oxorane, 1,3-dioxorane, 1,4-dioxane, thiorane, or the like. The above "cycloalkane" and "non-aromatic heterocycle" may be fused with other aromatic carbocycle such as benzene

or aromatic heterocycle such as thiophene or furan. Examples of heteroaryl fused with 4- to 7-membered cycloalkane or 4- to 7-membered non-aromatic heterocycle are illustrated below.



[0013] Examples of the substituent on "optionally substituted heteroaryl" include a group of the formula: $-Z^1-Z^2$ wherein Z^1 is a bond, -O-, -S-, -NH-,-NH-C(=O)-, -NH-C(=O)-O-, -NH-SO_2-, -C(=O)-, -O-C(=O)-, -C(=O)-O-, -SO_2-,-CH_2-O-, -CH_2-NH-C(=O)-, -CH_2-NH-C(=O)-O-, -CH_2-NH-SO_2-, or -CH_2-C(=O)-, and Z^2 is alkyl, haloalkyl, alkenyl, alkynyl, or optionally substituted amino; carboxy; halogen (F, Cl, Br, I); hydroxyalkyl; hydroxy; nitro; cyano; mercapto; thioformyl; thioacetyl; thiocarboxy; dithiocarboxy; thiocarbamoyl; sulfino; sulfo; sulfamoyl; sulfoamino and the like. A group of the formula: $-Z^1-Z^2$ wherein Z^1 is a bond, -O-, -S-, -NH-, -NH-C(=O)-, -NH-C(=O)-O-, -NH-SO_2-,-C(=O)-, -O-C(=O)-, -C(=O)-O-, -SO_2-, -CH_2-O-, -CH_2-NH-C(=O)-, -CH_2-NH-C(=O)-O-, -CH_2-NH-SO_2-, or -CH_2-C(=O)-, and Z^2 is alkyl or optionally substituted amino; carboxy; halogen; hydroxy; and nitro are preferred. Further, A group of the formula: $-Z^1-Z^2$ wherein Z^1 is a bond, -O-, -NH-C(=O)-,or -C(=O)-, and Z^2 is alkyl or optionally substituted amino; halogen; and hydroxy are preferred. One to three of the above substituents may be at any suitable position on the above heteroaryl.

[0014] "Alkyl" includes a straight or branched C1 to C8 alkyl group or a C3 to C8 cycloalkyl group. Examples are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A straight or branched C1 to C3 alkyl group is preferred.

[0015] "Haloalkyl" includes the above alkyl substituted with one to three halogen(s). A straight or branched C1 to C3 haloalkyl is preferred. Trifluoromethyl, 2,2,2-trifluoroethyl and the like are exemplified.

[0016] "Alkenyl" includes the above alkyl having one to three double bond(s). A straight or branched C2 to C3 alkenyl is preferred. Vinyl, allyl, 1-propenyl, isopropenyl and the like are exemplified.

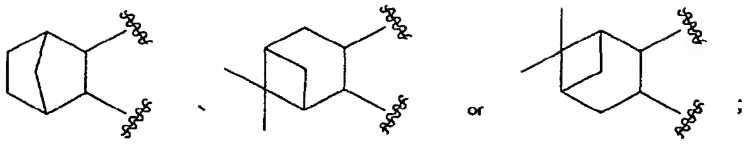
[0017] "Alkynyl" includes the above alkyl having one to three triple bond(s). A straight C2 to C3 alkynyl is preferred. Ethynyl and the like are preferred.

[0018] Examples of the substituent of "optionally substituted amino" include alkyl, alkyloxy, alkylsulfonyl, hydroxy, and the like. It may be mono- or disubstituted with these substituents.

[0019] "Hydroxy alkyl" includes the above alkyl substituted with one to three hydroxy. A straight or branched C1 to C3 hydroxyalkyl is preferred. Hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and the like are exemplified.

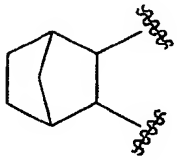
[0020] "Halogen" includes fluoro, chloro, bromo, and iodo.

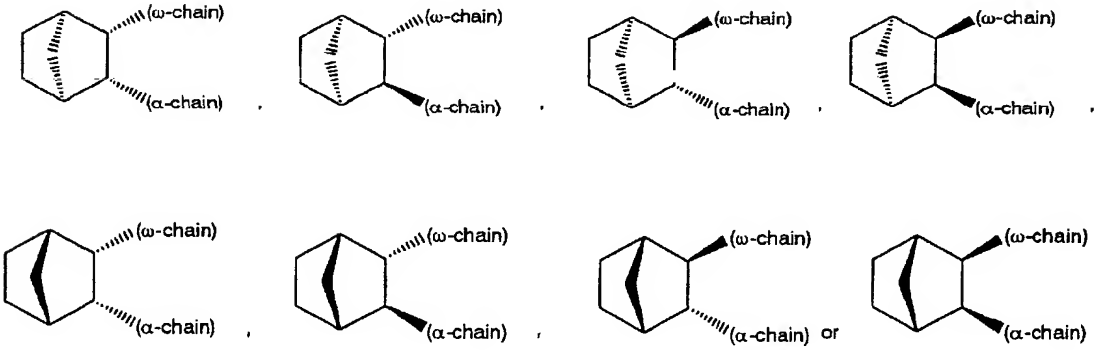
[0021] A compound of the present invention has the following [2.2.1] and [3.1.1] bicyclic skeleton.



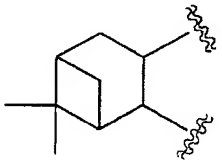
[0022] A compound of the present invention can be any of the following stereo isomers of [2.2.1] and [3.1.1] bicyclic skeleton.

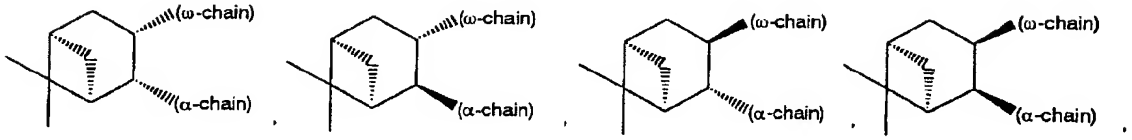
[0023] In a case of

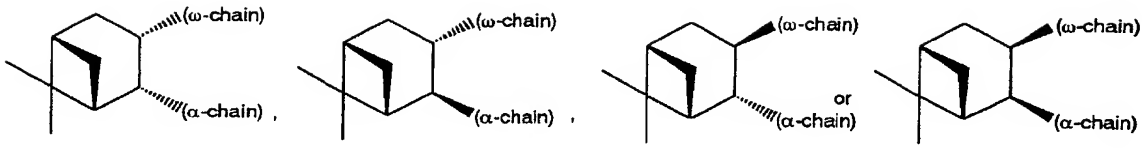




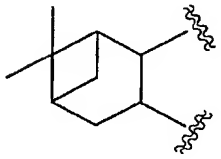
[0024] In a case of

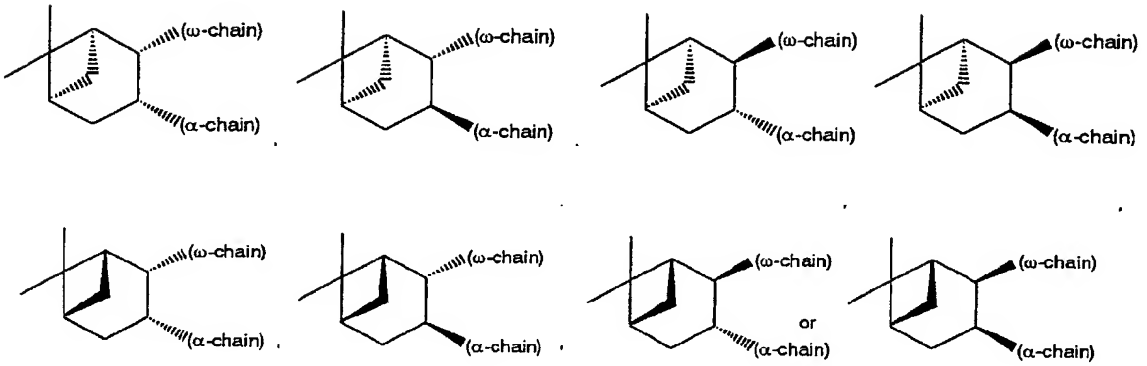




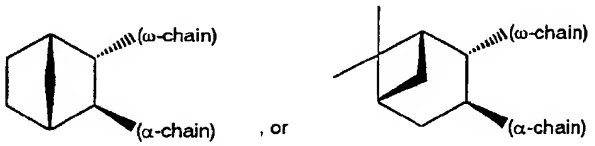


[0025] In a case of





[0026] In these stereo isomers, preferable is a compound having the skeleton of the formula:



[0027] The present invention includes all stereo isomers of them and the optional mixtures thereof. Namely, the bond binding to the bicyclic ring is in R configuration or S configuration, and all of the stereo isomers (diastereomer, epimer, enantiomer and the like), racemates, and optional mixture thereof are included in the present invention.

[0028] Moreover, the α chain of the compound of the present invention can be in Z configuration or E configuration, thus a compound having any of the configurations and the mixture thereof are included in the present invention.

[0029] Further, as the α chain (R^3) of the compound of the present invention, $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ and $-CH_2-CH_2-CH_2-CH_2-COOR^4$ (R^4 is hydrogen or alkyl; X^1 is -O- or -S-) are exemplified. Especially, $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ and $-CH_2-CH_2-CH_2-CH_2-COOR^4$ (R^4 is hydrogen; X^1 is -O- or -S-) are preferred. Further, $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$ and $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$ (R^4 is hydrogen; X^1 is -O- or -S-) are preferred.

[0030] This invention includes not only a compound represented by the formula (I), but also a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

[0031] A prodrug of a compound of the formula (I) is a derivative of the compound of the present invention having a group which can be decomposed chemically or metabolically, and such prodrug is converted to a pharmaceutically active compound of the present invention by means of solvolysis or by placing the compound in vivo under a physiological condition. Method for the selection and process of an appropriate prodrug derivative are described in the literature such as Design of Prodrugs, Elsevier, Amsterdam 1985.

[0032] When the compound of the formula (I) has a carboxyl group, an ester derivative prepared by reacting a basal acid compound with a suitable alcohol or an amide derivative prepared by reacting a basal acid compound with a suitable amine is exemplified as a prodrug. A particularly preferred ester derivative as an prodrug is an optionally substituted alkyl ester derivative (e.g., methyl ester, ethyl ester, n-propyl ester, isopropyl ester, n-butyl ester, isobutyl ester, tert-butyl ester, morpholinoethyl ester), an arylalkyl ester derivative (e.g., benzyl ester, phenethyl ester, benzhydryl ester), or the like. A particularly preferred amide derivative as a prodrug is alkyl amide derivative (e.g., N-methyl amide, N-ethyl amide, N-(n-propyl)amide, N-isopropyl amide, N-(n-butyl)amide, N-isobutyl amide, N-(tert-butyl)amide), aryl alkyl amide (e.g., N-benzyl amide, N-phenethyl amide, benzhydryl amide), or the like.

[0033] When the compound of the formula (I) has a hydroxy group, an acyloxy derivative prepared by reacting with a suitable acyl halide or a suitable acid anhydride is exemplified as a prodrug. A particularly preferred acyloxy derivative as a prodrug is a derivative substituted with optionally substituted alkylcarbonyloxy (e.g., $-OCOC_2H_5$, -OCO(tert-Bu), $-OCOC_{15}H_{31}$, $-OCOCH_2CH_2COONa$, $-OCOCH(NH_2)CH_3$, $-OCOCH_2N(CH_3)_2$-), optionally substituted arylcarbonyloxy (e.g., -OCO(m-COONa-Ph) or the like.

[0034] When the compound of the formula (I) has an amino group, an amide derivative prepared by reacting with a suitable acid halide or a suitable acid anhydride is exemplified as a prodrug. A particularly preferred amide derivative as a prodrug is a derivative substituted with optionally substituted alkylcarbonyl (e.g., $-NHCO(CH_2)_{20}CH_3$, $-NHCOCH(NH_2)CH_3$) or the like.

[0035] Examples of a salt of the compound of the formula (I) or its prodrug include alkali metal salts such as lithium salts, sodium salts or potassium salts, alkaline-earth metal salts such as calcium salts, salts with organic bases such as tromethamine, trimethylamine, triethylamine, 2-aminobutane, tert-butylamine, diisopropylethylamine, n-butylmethylamine, cyclohexylamine, dicyclohexylamine, N-isopropylcyclohexylamine, furfurylamine, benzylamine, methylbenzylamine, dibenzylamine, N,N-dimethylbenzylamine, 2-chlorobenzylamine, 4-methoxybenzylamine, 1-naphthylene methylamine, diphenylbenzylamine, triphenylamine, 1-naphthylamine, 1-aminoanthorathene, 2-aminoanthorathene, dehydroabiethylamine, N-methylmorpholine, pyridine), basic amino acid salts such as arginine salts or lysine salts.

[0036] A solvate means a solvate with an organic solvent, a hydrate and the like of the compound of the formula (I), its prodrug or its pharmaceutically acceptable salt, for example, monohydrate, dihydrate or the like.

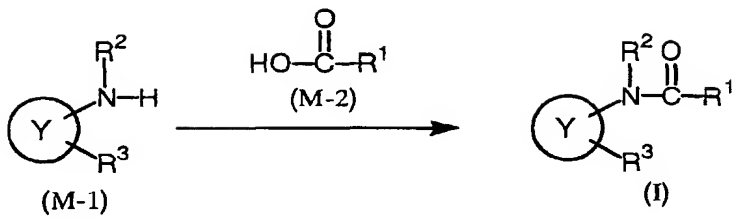
[0037] "A pharmaceutical composition having an antagonistic activity against PGD_2 receptor" means a pharmaceutical composition comprising at least one compound of the formula (I) having an antagonistic activity against a PGD_2 receptor. In addition to a compound of the formula (I), the other active agents (e.g. antiinflammatory agents, antiallergy agents and the like) and pharmaceutically acceptable admixtures (e.g., binding agent, filler and the like) may be included.

[0038] A PGD_2 antagonist is useful in the improvement of conditions due to excessive production of PGD_2, particularly as a composition for treating diseases in which mast cell dysfunction is involved, for example, systemic mastocytosis and disorder of systemic mast cell activation as well as for nasal blockage, allergic conjunctivitis, allergic rhinitis, airway contraction, asthma, urticaria, ischemic reperfusion injury, inflammation, and atopic dermatitis.

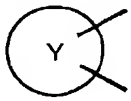
[0039] This invention includes a method for treating a condition due to excessive production of PGD_2 such as nasal blockage, allergic conjunctivitis, allergic rhinitis, and the like, which comprises administrating a compound represented by the formula (I). In addition, this invention includes use of the compound represented by the formula (I) for the preparation of a pharmaceutical composition for treating a condition due to excessive production of PGD_2 such as nasal blockage, allergic conjunctivitis or allergic rhinitis.

Best Mode for Carrying Out the Invention

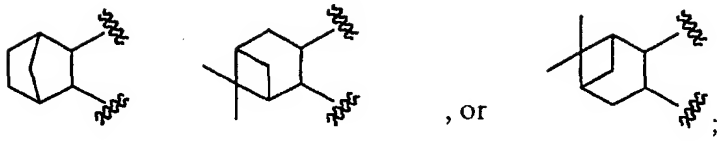
[0040] The compound represented by the formula (I) can be prepared in accordance with the following method.



wherein



is



R^1 is optionally substituted heteroaryl;
R^2 is hydrogen or alkyl;
R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$;
R^4 is hydrogen or alkyl; and
X^1 is -O- or -S-.

[0041] As shown in the above process, the compound of the formula (I) can be prepared by reacting a carboxylic acid of the formula (M-2) or its reactive derivative with an amino compound of the formula (M-1).

[0042] The reactive derivatives of carboxylic acid of the formula (M-2) mean the corresponding acid halides (e.g., chloride, bromide, iodide), anhydrides (e.g., mixed anhydride with formic acid or acetic acid), active esters (e.g., N-hydroxysuccinimide ester), and the like, and include acylating agents used for the usual acylation of amino group.

[0043] For example, an acid halide is obtained by reacting the compound (M-2) with a thionyl halide (e.g., thionyl chloride), phosphorous halide (e.g., phosphorous trichloride, phosphorous pentachloride), oxalyl halide (e.g., oxalyl chloride), and the like, in accordance with known methods as described in the literatures.

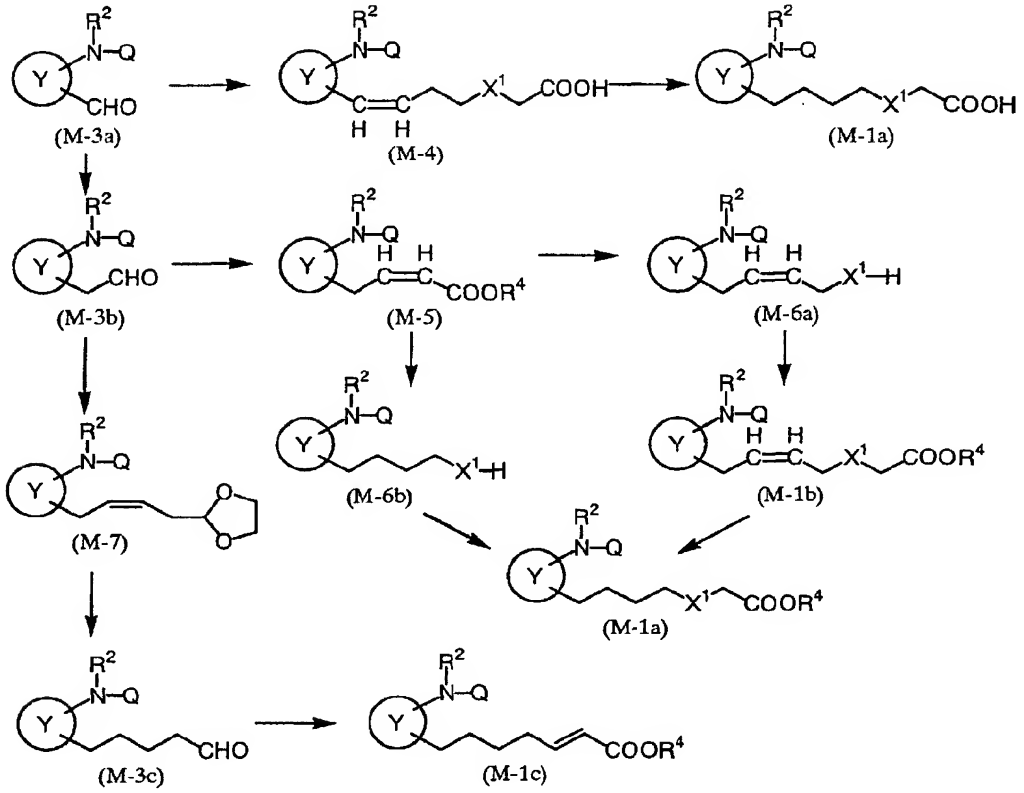
[0044] The reaction can be conducted under a condition generally used for the acylation of amino group. For example, in the case of condensation with the acid halide, the reaction is carried out in a solvent such as an ether solvent (e.g., diethyl ether, tetrahydrofuran, dioxane), benzene solvent (e.g., benzene, toluene, xylene), halogenated hydrocarbon solvent (e.g., dichloromethane, dichloroethane, chloroform) as well as ethyl acetate, dimethylformamide, dimethyl sulfoxide, acetonitrile, or the like, if necessary, in the presence of a base (e.g., organic base such as triethylamine, pyridine, N,N-dimethylaminopyridine, N-methylmorpholine; inorganic base such as sodium hydroxide, potassium hydroxide, potassium carbonate, or the like) under cooling, at room temperature, or under heating, preferably at a temperature ranging from -20 °C to ice-cooling temperature, or from room temperature to a refluxing temperature of the reaction system, during several min to several hr, preferably for 0.5 hr to 24 hr, more preferably for 1 hr to 12 hr.

[0045] When R^4 is alkyl, a free form may be used without converting the carboxy group (M-2) into the reactive derivatives and the reaction may be conducted in the presence of a condensing agent (e.g., dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-methylaminopropyl)carbodiimide, N,N'-carbonyldiimidazole, or the like) usually used in the condensation reaction of amine and carboxylic acid.

[0046] When the substituent of "optionally substituted aryl" or "optionally substituted heteroaryl" of the compound of the formula (M-2) is substituted with a hydroxy group, an amino group or the like, such a compound can be used after

protection by acetyl group or the like in accordance with the well known method.

[0047] In the reaction of the other reactive derivatives or free acid (M-2) with the amine (M-1), the reaction conditions are determined according to the property of each reactive derivative or free acid, in accordance with a known method. The reaction product can be purified in accordance with a conventional purification, such as the extraction with a solvent, chromatography, recrystallization, and the like.



wherein Q is a protective group of an amino group; R^2, X^1 and R^4 are as defined above.

[0048] The compounds represented by formula (M-1) can be prepared from the aldehyde derivative (Q is a protecting group such as benzyloxycarbonyl, t-butoxycarbonyl and the like) represented by a general formula (M-3a) or (M-3b) by one or more reaction(s) of a ylide compound under a Wittig reaction condition (Org. Reaction, 1965, 14, 270) in combination with other reactions.

[0049] For example, the aldehyde (M-3a) is reacted with phosphonium salt derived from 6-bromo-3-oxahexanoic acid described in WO97/40104 under a well known Wittig reaction condition to give a compound (M-4). The compound (M-4) is hydrogenated in the presence of palladium, platinum and the like to give a starting material (M-1a, X^1=O), wherein R^3 is-$CH_2CH_2CH_2CH_2OCH_2COOR^4$. Furthermore, after Wittig reaction using methoxymethyltriphenyl-phosphonium salt, followed by a hydrolysis with hydrochloric acid, formic acid, acetic acid and the like can furnish an aldehyde (M-3b). Under Wittig reaction condition using a stable ylide such as methyl (triphenylphophoranidene)acetate and the like or Honer-Emmons reaction condition using methyl dimethylphosphonoacetate, the above aldehyde can be converted into α,β-unsaturated carboxylic acid derivative represented by the formula (M-5). An alcohol derivative (M-6a, X^1=O) which is obtained by reduction of compound (M-5) is reacted with halogenated acetic acid or its ester derivative in accordance with well known methods to give a starting compound (M-1b, X^1=O) wherein R^3 is -CH_2CH=$CHCH_2OCH_2COOR^4$. Further, after an alcohol derivative (M-6a, X^1=O) is converted into a thiol derivative (X^1=S) in accordance with well known methods, the obtained compound is reacted with halogenated acetic acid derivative as shown the above to give a starting compound (M-1b, X^1=S) wherein R^3 is -CH_2CH=$CHCH_2SCH_2COOR^4$. Also, after an alcohol derivative (M-6a, X^1=O) is converted into a halogenated derivative in accordance with well known methods, the obtained compound is reacted with a glycolic acid or a thioglycollic acid in the presence of a base to give the above compound (M-1b X^1=S). The double bonds in the R^3 can be reduced by hydrogenation in the presence of

catalyst such as palladium, platinum, and the like at the suitable stage to give a corresponding saturated derivative (M-1a X^1=O or S) at ease.

[0050] The aldehyde (M-3b) is converted into a compound represented by the formula (M-7) by Wittig reaction using 2-(1,3-dioxolane-2-yl)ethyltriphenylphosphonium salt. A hydrogenation of the compound (M-7) and an acidic hydrolysis of acetal are carried out to give the aldehyde (M-3c) as shown in the above. Under Wittig reaction condition using a stable ylide such as methyl (triphenylphophoranidene)acetate and the like or Honer-Emmons reaction condition using methyl dimethylphosphonoacetate, the above aldehyde (M-3c) can be converted into a starting compound (M-1c) wherein R^3 corresponds to $-CH_2CH_2CH_2CH_2CH=CHCOOR^4$.

[0051] Amidation with a starting carboxylic acid (M-2) can be accomplished after a deprotection of an amino protecting group Q in a way of conversion to α-chain, if necessary.

[0052] In case of the introduction of a substituent(s) into the "optionally substituted aryl" or "optionally substituted heteroaryl", the change of the functional group can be performed before or after reacting a carboxylic acid or its reactive derivative thereof (M-2) with the amine (M-1). For example, the compound having an aromatic heterocycle substituted with a nitro group can be prepared through the nitration of the compound with a nitrating acid. Moreover, the compound having an aromatic heterocycle substituted with an amino group can be prepared through the reduction of the above-obtained compound with tin in the presence of hydrochloride. Moreover, the compound having an aromatic heterocycle substituted with a hydroxy group can be prepared through the diazonization of the above-obtained compound and the hydrolysis with alkali. On the other hand, the compound having an aromatic heterocycle substituted with an alkoxy group can be prepared through the reaction of the diazonium derivative with alcohol. The compound having an aromatic heterocycle substituted with halogen can be prepared through Sandmeyer reaction, the reaction of the diazonium derivative with a copper salt (e.g., $CuCl_2$, $CuBr_2$). The compound having an aromatic heterocycle substituted with halogen can be also prepared through the direct reaction of the compound having an aromatic heterocycle with chlorine and the like. Using the above-mentioned methods appropriately, halogen can be introduced into a desired position(s). The group of alkyl, alkenyl or acyl group can be directly introduced into an aromatic heterocycle through Friedel Crafts reaction with alkylating agent, an alkenylating agent, or an acylating agent, respectively, in the presence of anhydrous aluminum chloride and the like.

[0053] When using the compound (I) of the present invention in treatment, it can be formulated into ordinary formulations for oral and parenteral administration. A pharmaceutical composition containing the compound (I) of the present invention can be in the form for oral and parenteral administration. Specifically, it can be formulated into formulations for oral administration such as tablets, capsules, granules, powders, syrup, and the like; or those for parenteral administration such as injectable solution or suspension for intravenous, intramuscular, or subcutaneous injection, inhalant, eye drops, nasal drops, suppositories, or percutaneous formulations such as ointment.

[0054] In preparing the formulations, carriers, excipients, solvents, and bases known to one having ordinary skill in the art may be used. In case of tablets, they are prepared by compressing or formulating an active ingredient together with auxiliary components. Examples of usable auxiliary components include pharmaceutically acceptable excipients such as binders (e.g., cornstarch), fillers (e.g., lactose, microcrystalline cellulose), disintegrants (e.g., starch sodium glycolate) or lubricants (e.g., magnesium stearate). Tablets may be coated appropriately. In case of liquid formulations such as syrups, solutions, or suspensions, they may contain suspending agents (e.g., methyl cellulose), emulsifiers (e.g., lecithin), preservatives. and the like. In case of injectable formulations, it may be in the form of solution, suspension, or oily or aqueous emulsion, which may contain suspension-stabilizing agents or dispersing agent, and the like. In case of an inhalant, it is formulated into a liquid formulation applicable to an inhaler. In case of eye drops, it is formulated into a solution or a suspension.

[0055] Especially, in case of a nasal drug for treating nasal blockage, it can be used as a solution or suspension prepared by a conventional formulating method, or administered as a powder formulated using a powdering agent (e.g., hydroxypropyl cellulose, carbopole) into the nasal cavity. Alternatively, it can be used as an aerosol filled into a special container together with a solvent of low boiling point.

[0056] In a case using as an eyewash drug for treating allergic conjunctivitis, it can be used as a solution or suspension of the compound or can be used by solving or suspending the compound before use. A stabilizing agent, solubilizing agent, suspending agent, emulsifier, buffer, preservatives and the like can be included. In a case using as an eyewash drug, aseptic treatment is preferable.

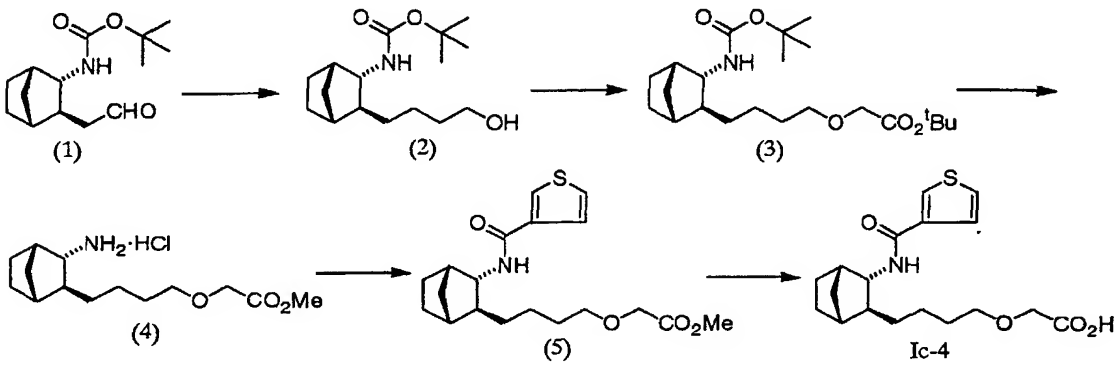
[0057] Although an appropriate dosage of the compound (I) varies depending on the administration route, age, body weight, sex, or conditions of the patient, and the kind of drug(s) used together, if any, and should be determined by the physician in the end, in the case of oral administration, the daily dosage can generally be between 0.01 - 100 mg, preferably 0.01 - 10 mg, more preferably 0.01 - 1 mg, per kg body weight. In case of parenteral administration, the daily dosage can generally be between 0.001 - 100 mg, preferably 0.001 - 1 mg, more preferably 0.001 - 0. 1 mg, per kg body weight. The daily dosage can be administered in 1 - 4 divisions.

Example

[0058] The following examples are provided to further illustrate the present invention and are not to be construed as limiting the scope.

Example 1 Preparation of (Ic-4)

[0059]



Process 1

[0060] To a solution of compound (1) (10.11g, 39.9mmol) in toluene (100ml) was added triphenylphosphoranylidene acetic acid methyl ester (14.68g, 43.9mmol) and the resulting mixture was stirred for 17 h at room temperature. Hexane (100ml) was added to the mixture and the insoluble residue was filtered off.
The filtration was concentrated to give 16.56g of residue. 16.12g of the residue was dissolved in THF(160ml), 2N lithium hydroxide aq. (40ml) was added to the solution and the resulting mixture was stirred for 5h at 60°C.
After THF was concentrated in vacuo, the residue was diluted with water (100ml). The water layer was washed with toluene twice and acidified with hydrochloric acid (pH=1) and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, and concentrated. To a solution of the residue in methanol was added 10% palladium-carbon (360mg) and the resulting mixture was stirred for 3h under hydrogen atmosphere. The reaction mixture was filtered and concentrated and the residues was dissolved in THF (120ml). To the mixture were added triethylamine (6.2ml, 44.5mmol) and ethyl chloroformate (4.3ml, 44.5mmol) at ice-cooling, and the resulting mixture was stirred for 30 min at ice-cooling. The insoluble salt was filtered off and sodium borohydride (3.06g, 80.9mmol) was added to the filtration. To the mixture was added methanol (40ml) dropwise over 30 min and the mixture was stirred for 30 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine respectively and dried. The residue was crystallized from hexane-ethyl acetate (90:10) to give compound (2) (8.77g; yield 80%). mp. 90-92°C.

Process 2

[0061] To a solution of the compound (2) (1.68g, 5.94mmol) in toluene (17ml) were added t-butyl bromoacetate (1.32ml, 68.91mmol), sodium hydrogensulfate (201mg, 0.6mmol) and 50% sodium hydroxide aq. (1.7ml) and the resulting mixture was vigorously stirred for 22h at room temperature. Toluene layer was separated, washed with water and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=7:1) to give compound (3) (1.60g; yield 68%).

Process 3

[0062] To a solution of the compound (3) (10.42g, 26.2mmol) in methanol (50ml) was added 4N dioxane solution of hydrogen chloride (65.5ml, 262mmol) and the resulting mixture was stirred for 5h at room temperature. The reaction mixture was concentrated in vacuo to give crystalline residue. The residue was washed with hexane-ether to give compound (4) (6.88g; yield 90%).

Process 4

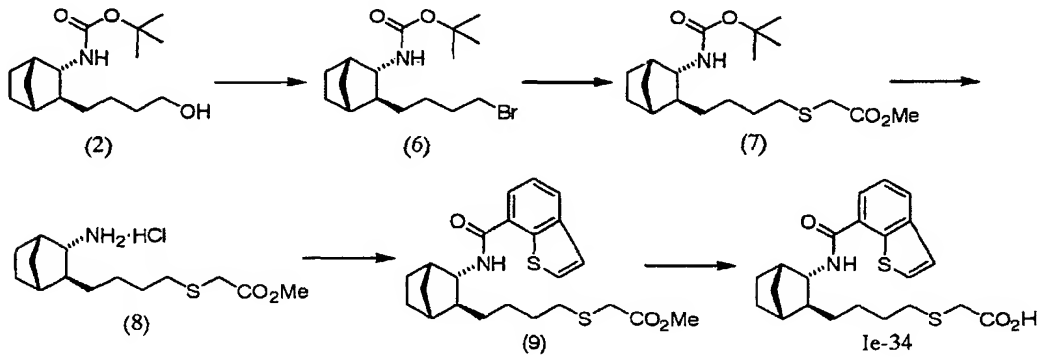
[0063] To a solution of compound (4)(642mg, 2.20mmol) in THF (8ml) were added thiophene-3-carboxylic acid (256mg, 2.00mmol), 1-hydroxybenzotriazole (27mg, 0.20mmol) and triethylamine (0.34ml, 2.40mmol) at ice-cooling. Further, 3-ethyl-3-(3-dimethylaminopropyl)carbodiimide (370mg, 2.40mmol) was added to the mixture at ice-cooling. The reaction mixture was stirred for 16h at room temperature and diluted with ethyl acetate. The resulting mixture was washed with dilute hydrochloric acid and sodium hydrogencarbonate respectively, dried, concentrated, and chromatographed on silica gel (toluene-hexane=3:1) to give compound (5) (627mg; yield 86%). m.p. 68-70°C.

Process 5

[0064] To a solution of compound (5) (620mg, 1.70mmol) in methanol (2ml)-THF (1ml) was added 4N sodium hydroxide aq.(1.0ml, 4.0mmol) and the resulting mixture was stirred for 16h at room temperature. The reaction mixture was acidified with 2N hydrochloric acid. and extracted with ethyl acetate. The organic layer was washed with water and brine respectively, dried and concentrated. The residue was crystallized from methanol-water (5:7) to give compound (Ic-4) (461mg; yield 77%). m.p. 104-105°C.

Example 2 Preparation of compound (Ie-34)

[0065]



Process 1

[0066] To a solution of compound (2) (2.28g, 8.05mmol) in dichloromethane (20ml) were added triphenylphosphine (2.32g, 8.85mmol) and N-bromosuccinimide (1.58g, 8.85mmol) at ice-cooling and the resulting mixture was stirred for 1h at the same temperature. The reaction mixture was diluted with toluene, washed with water and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=9:1) to give compound (6) (2.70g; yield 97%).

Process 2

[0067] To a solution of sodium methoxide (842mg, 15.6mmol) in methanol (20ml) was added methyl thioglycolate (1.40ml, 15.6mmol) and the resulting mixture was stirred for 15 min at room temperature. To the mixture was added a THF (20ml) solution of compound (6) (2.70g, 7.80mmol) and the resulting mixture was stirred for 15 h. The reaction was diluted with ethyl acetate, washed with water and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=78:22) to give compound (7) (2.84g; yield 98%).

Process 3

[0068] 4N Ethyl acetate solution of hydrogen chloride (15 ml) was added to compound (7) (2.84g, 7.64mmol) and the resulting mixture was stirred for 2h at room temperature. The reaction mixture was concentrated in vacuo to give the residue. The residue was crystallized from hexane-ether to give compound (8) (2.16g; yield 92%).

Process 4

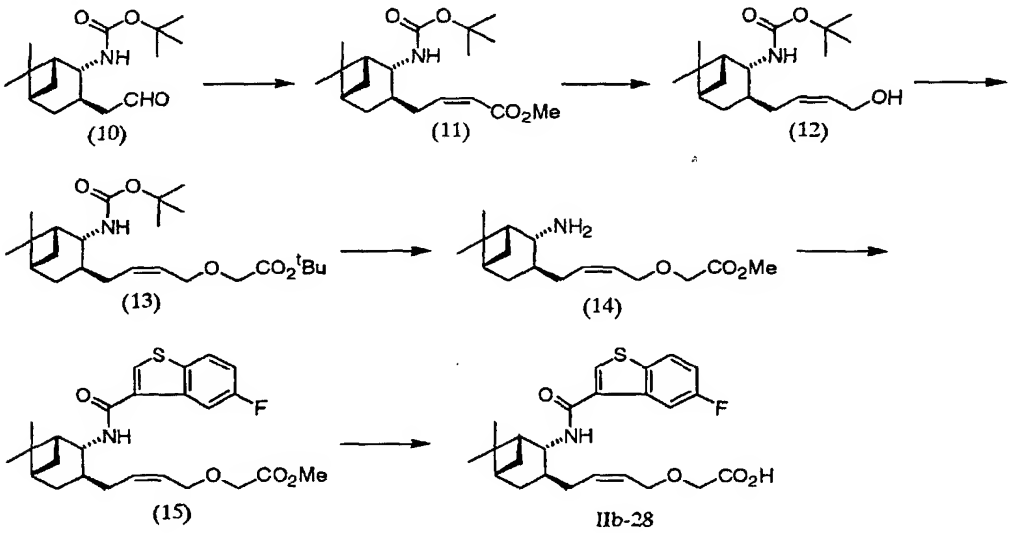
[0069] To a solution of compound (8) (246mg, 0.80mmol) in THF (6ml) were added benzothiophene-7-carboxylic acid (150mg, 0.80mmol), 1-hydroxybenzotriazole (11mg, 0.08mmol), triethylamine (0.12ml, 0.96mmol) at ice-cooling. Further, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (149mg, 0.96mmol) was added to the mixture at ice-cooling. The reaction mixture was stirred for 16h at room temperature and diluted with ethyl acetate. The resulting mixture was washed with dilute hydrochloric acid and sodium hydrogencarbonate aq. respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=3:1) to give compound (9) (324mg; yield 94%).

Process 5

[0070] To a solution of compound (9) (315mg, 0.73mmol) in THF (3.6ml)-methanol (7.3 ml) was added 1N sodium hydroxide aq.(1.82ml, 1.82mmol) and the resulting mixture was stirred for 48h at room temperature. The reaction mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine respectively to give compound (Ie-34) (301mg; yield 99%).

Example 3 Preparation of compound (IIb-28)

[0071]



Process 1

[0072] A solution of methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (3.0ml, 14.3mmol) and 18-crown-6 (5.64g, 21.3mmol) in THF (100ml) was cooled at-55°C and bis(trimethylsilyl)amide potassium (0.5M toluene solution, 28.5ml, 14.3mmol) was added dropwise to the mixture. The resulting mixture was stirred for 15 min. To the mixture was added a solution of compound (10) (2.0g, 7.11mmol) in THF (20ml) was added dropwise over 15 min and the mixture was stirred for 1h at the same temperature. The reaction mixture was allowed to warm to 0°C, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=4:1) to give compound (11) (2.16g; yield 90%).

Process 2

[0073] A solution of compound (11) (1.37g, 4.05mmol) in dichloromethane (10ml)-hexane (10ml) was cooled to -60°C and diisopropylaluminum hydride (0.95M hexane solution, 10.7ml, 10.2mmol) was added dropwise to the solution. The mixture was stirred for 30 min at the same temperature and methanol (0.6ml) was added. The resulting mixture was allowed to warm to room temperature and 2N hydrochloric acid was added. The mixture was extracted with ethyl

acetate and the organic layer was washed with sodium hydrogencarbonate aq. and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=2:1) to give compound (12) (1.14g; yield 91%). m.p. 67-69°C.

Process 3

[0074] To a solution of compound(12) (1.03g, 3.31mmol) in toluene (10ml) were added t-butyl bromoacetate (0.70ml, 4.30mmol), tetrabutylammonium hydrogensulfate (170mg, 0.5mmol), and 50% sodium hydroxide (1.5ml) and the resulting mixture was vigorously stirred for 18h at room temperature. The reaction mixture was extracted with toluene, washed with water and brine respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=4:1) to give compound (13) (1.32g; yield 94%).

Process 4

[0075] To a solution of compound (13) (1.3g, 3.07mmol) in toluene (3ml) was added trifluoroacetic acid (3.5ml, 46mmol) and the resulting mixture was stirred for 3.5h at 65°C. The reaction mixture was concentrated in vacuo and methanol (30ml) and concentrated sulphuric acid (0.33ml) were added to the mixture. The resulting mixture was stirred for 1h at reflux. The reaction mixture was concentrated and the residue was dissolved in toluene. To the mixture was added triethylamine (4.3ml, 30mmol) and sodium hydrogencarbonate aq. respectively. The toluene layer was separated, washed with water and brine respectively, dried, and concentrated to give compound (14) (697mg; yield 81%).

Process 5

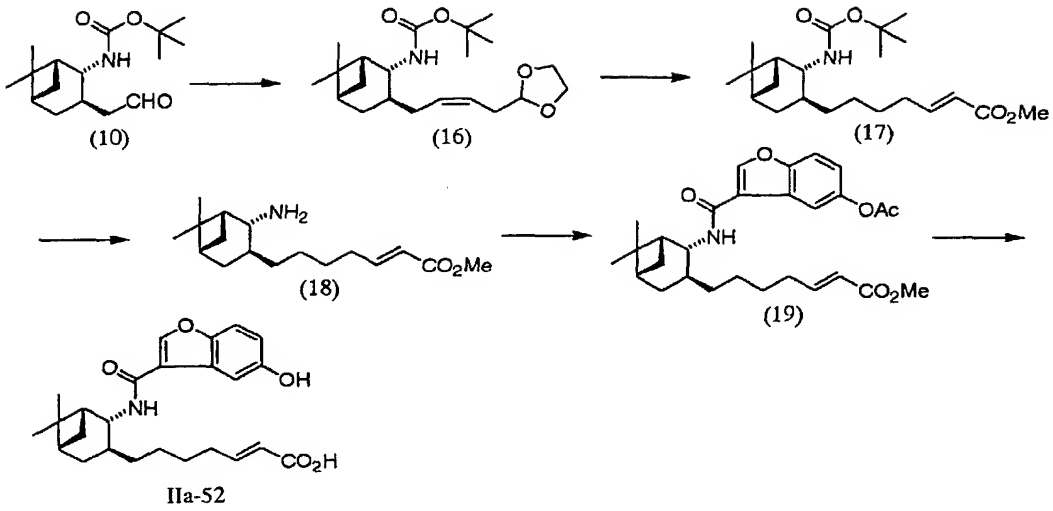
[0076] To a solution of compound(14) (141mg, 0.50mmol) in THF (4ml) were added 5-fluorobenzothiophene-3-carboxylic acid (98mg, 0.50mmol) and 1-hydroxybenzotriazole (7mg, 0.05mmol) at ice-cooling. Further, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (93mg, 0.6mmol) was added at the same temperature. The reaction mixture was stirred for 16h at room temperature, diluted with ethyl acetate, washed with dilute hydrochloric acid and sodium hydrogencarbonate aq. respectively, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=83:17) to give compound (15) (93mg; yield 40%).

Process 6

[0077] To a solution of compound (15)(93mg, 0.20mmol) in THF (1ml)-methanol (2ml) was added 1N sodium hydroxide aq.(0.5ml, 0.5mmol) and the resulting mixture was stirred for 18h at room temperature. The reaction mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine respectively to give compound (IIb-28) (82mg; yield 91%).

Example 4 Preparation of compound(IIa-52)

[0078]



Process 1

[0079] A suspension of 2-(1,3-dioxorane-2-yl)ethyltriphenylphosphonium bromide (13.28g, 30.0mmol) in THF (60ml) was cooled to -30°C and potassium t-butoxide (6.73g, 60.0mmol) was added. The mixture was stirred for 1h at-30°C to 0°C and allowed to cool to -25°C. To the mixture was added a solution of compound (10) (5.62g, 20.0mmol) in THF (40ml) dropwise over 15 min. The reaction mixture was allowed to warm to 0°C, stirred for additional 1.5h, diluted with water. The water layer was extracted with ethyl acetate and the extract is washed with water and brine, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=85:15) to give compound (16) (6.27g; yield 86%).

Process 2

[0080] A solution of compound (16) (4.10g, 11.2mmol) in methanol (41ml) was stirred for 2h in the presence of 10% palladium-carbon (0.21g) under hydrogen atmosphere. The reaction mixture was filtered and concentrated to give a residue (4.12g; yield 100%). To a solution of the crude compound (3.68g, 10.0mmol) in acetone-water (4:1, 50ml) was added pyridinium p-toluenesulfonate (503mg, 2.0mmol) and the mixture was heated for 6h at reflux. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried, concentrated. A solution of the residue in toluene (35ml) was added methyl (triphenylphosphoranylidene)acetate (2.93g, 8.76mmol) and the resulting mixture was stirred for 18h at room temperature. The mixture was diluted with ethyl acetate, washed with water and brine, dried, concentrated, and chromatographed on silica gel (hexane-ethyl acetate=85:15) to give compound (17) (2.71g; yield 71%).

Process 3

[0081] To a solution of compound (17) (2.35g, 6.19mmol) in dichloromethane (38ml) was added trifluoroacetic acid (3.82ml, 49.5mmol) and the resulting mixture was stirred for 3h at room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in toluene (50ml) and water (10ml). The water layer was alkalinized with 2N sodium hydroxide (pH=10). Toluene layer was separated, washed with water and brine, dried, and concentrated to give compound (18) (1.70g, yield 98%).

Process 4

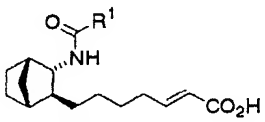
[0082] To a solution of compound (18) (280mg, 1.0mmol) in THF(5ml) were added 5-acetoxybenzofuran-3-carboxylfic acid (220mg, 1.0mmol), 1-hydroxybenzotriazole (13mg, 0.1mmol). Further, 1-ethyl-3-(3-dimethylaminopropyl)carbod-

iimide (200mg, 1.3mmol) was added at ice-cooling. After the reaction mixture was stirred for 16h at room temperature, the mixture was diluted with toluene, washed with dilute hydrochloric acid and sodium hydrogencarbonate aq. respectively, dried, and concentrated. The residue was chromatographed on silica gel (hexane-ethyl acetate=3:1) to give compound (19) (422mg; yield 88%). m.p. 119-120°C.

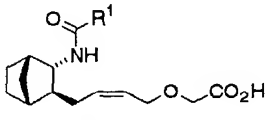
Process 5

[0083] To a solution of compound (19) (422mg, 0.88mmol) in THF (5.6ml) was added IN lithium hydroxide aq. (3.0ml, 3.0mmol) and the resulting mixtur was stirred for 20h at room temperature. The reaction mixture was acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and brine respectively, dried, and concentrated. The residue was crystallized from hexane-ethyl acetate to give compound (IIa-52) (327mg; yield 87%). m.p. 159-160°C.

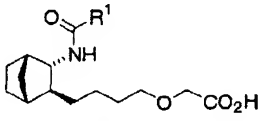
[0084] The structure and physical property of the compound prepared in accordance with the above examples are shown below. Each sign such as Ia, Ib,,, IIe, and IIf used in the following Tables means the partial structure represented below:



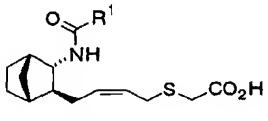
Ia



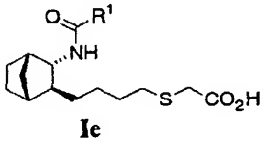
Ib



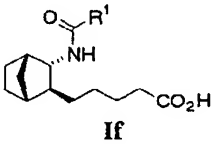
Ic



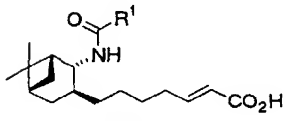
Id



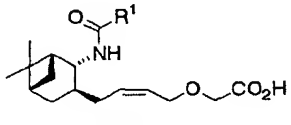
Ie



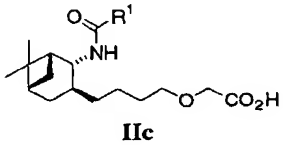
If



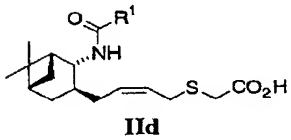
IIa



IIb



IIc



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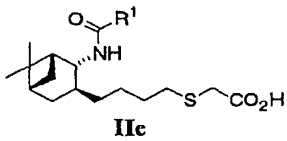
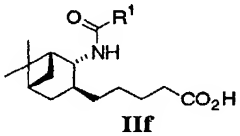
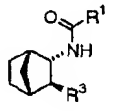


IIe



IIf

Table 1

R^1 	Ia	Ib	Ic	Id	Ie	If
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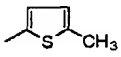
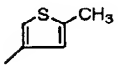
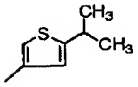
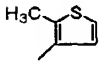
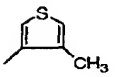
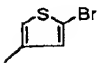
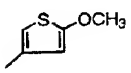
	Ia-2	Ib-2	Ic-2	Id-2	Ie-2	If-2
	Ia-3	Ib-3	Ic-3	Id-3	Ie-3	If-3
	Ia-4	Ib-4	Ic-4	Id-4	Ie-4	If-4
	Ia-5	Ia-5	Ic-5	Id-5	Ie-5	If-5
	Ia-6	Ib-6	Ic-6	Id-6	Ie-6	If-6
	Ia-7	Ib-7	Ic-7	Id-7	Ie-7	If-7
	Ia-8	Ib-8	Ic-8	Id-8	Ie-8	If-8
	Ia-9	Ib-9	Ic-9	Id-9	Ie-9	If-9
	Ia-10	Ib-10	Ic-10	Id-10	Ie-10	If-10

Table 2

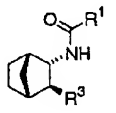
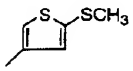
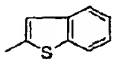
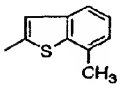
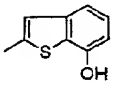
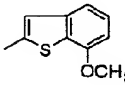
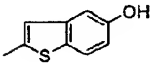
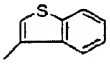
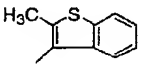
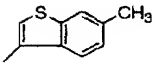
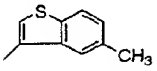
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-11	Ib-11	Ic-11	Id-11	Ie-11	If-11
	Ia-12	Ib-12	Ic-12	Id-12	Ie-12	If-12
	Ia-13	Ib-13	Ic-13	Id-13	Ie-13	If-13
	Ia-14	Ib-14	Ic-14	Id-14	Ie-14	If-14
	Ia-15	Ia-15	Ic-15	Id-15	Ie-15	If-15
	Ia-16	Ib-16	Ic-16	Id-16	Ie-16	If-16
	Ia-17	Ib-17	Ic-17	Id-17	Ie-17	If-17
	Ia-18	Ib-18	Ic-18	Id-18	Ie-18	If-18
	Ia-19	Ib-19	Ic-19	Id-19	Ie-19	If-19
	Ia-20	Ib-20	Ic-20	Id-20	Ie-20	Ief-20

Table 3

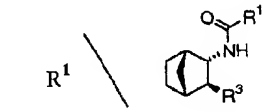
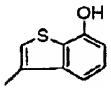
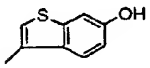
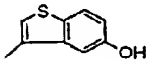
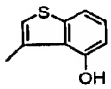
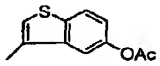
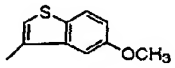
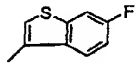
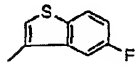
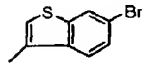
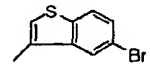
	Ia	Ib	Ic	Id	Ie	If
	Ia-21	Ib-21	Ic-21	Id-21	Ie-21	If-21
	Ia-22	Ib-22	Ic-22	Id-22	Ie-22	If-22
	Ia-23	Ib-23	Ic-23	Id-23	Ie-23	If-23
	Ia-24	Ib-24	Ic-24	Id-24	Ie-24	If-24
	Ia-25	Ia-25	Ic-25	Id-25	Ie-25	If-25
	Ia-26	Ib-26	Ic-26	Id-26	Ie-26	If-26
	Ia-27	Ib-27	Ic-27	Id-27	Ie-27	If-27
	Ia-28	Ib-28	Ic-28	Id-28	Ie-28	If-28
	Ia-29	Ib-29	Ic-29	Id-29	Ie-29	If-29
	Ia-30	Ib-30	Ic-30	Id-30	Ie-30	If-30

Table 4

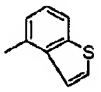
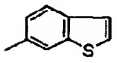
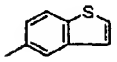
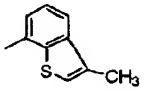
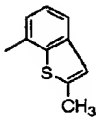
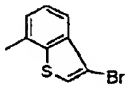
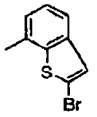
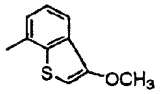
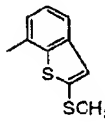
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-31	Ib-31	Ic-31	Id-31	Ie-31	If-31
	Ia-32	Ib-32	Ic-32	Id-32	Ie-32	If-32
	Ia-33	Ib-33	Ic-33	Id-33	Ie-33	If-33
	Ia-34	Ib-34	Ic-34	Id-34	Ie-34	If-34
	Ia-35	Ia-35	Ic-35	Id-35	Ie-35	If-35
	Ia-36	Ib-36	Ic-36	Id-36	Ie-36	If-36
	Ia-37	Ib-37	Ic-37	Id-37	Ie-37	If-37
	Ia-38	Ib-38	Ic-38	Id-38	Ie-38	If-38
	Ia-39	Ib-39	Ic-39	Id-39	Ie-39	If-39
	Ia-40	Ib-40	Ic-40	Id-40	Ie-40	If-40

Table 5

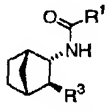
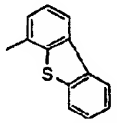
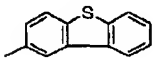
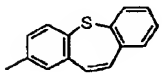
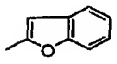
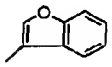
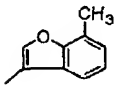
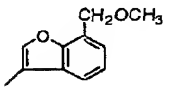
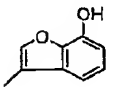
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-41	Ib-41	Ic-41	Id-41	Ie-41	If-41
	Ia-42	Ib-42	Ic-42	Id-42	Ie-42	If-42
	Ia-43	Ib-43	Ic-43	Id-43	Ie-43	If-43
	Ia-44	Ib-44	Ic-44	Id-44	Ie-44	If-44
	Ia-45	Ia-45	Ic-45	Id-45	Ie-45	If-45
	Ia-46	Ib-46	Ic-46	Id-46	Ie-46	If-46
	Ia-47	Ib-47	Ic-47	Id-47	Ie-47	If-47
	Ia-48	Ib-48	Ic-48	Id-48	Ic-48	If-48
	Ia-49	Ib-49	Ic-49	Id-49	Ie-49	If-49
	Ia-50	Ib-50	Ic-50	Id-50	Ie-50	If-50

Table 6

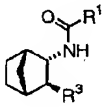
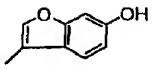
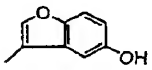
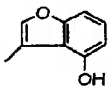
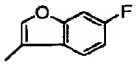
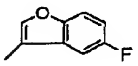
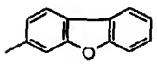
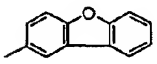
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-51	Ib-51	Ic-51	Id-51	Ie-51	If-51
	Ia-52	Ib-52	Ic-52	Id-52	Ie-52	If-52
	Ia-53	Ib-53	Ic-53	Id-53	Ie-53	If-53
	Ia-54	Ib-54	Ic-54	Id-54	Ie-54	If-54
	Ia-55	Ia-55	Ic-55	Id-55	Ie-55	If-55
	Ia-56	Ib-56	Ic-56	Id-56	Ie-56	If-56
	Ia-57	Ib-57	Ic-57	Id-57	Ie-57	If-57
	Ia-58	Ib-58	Ic-58	Id-58	Ie-58	If-58
	Ia-59	Ib-59	Ic-59	Id-59	Ie-59	If-59
	Ia-60	Ib-60	Ic-60	Id-60	Ie-60	If-60

Table 7

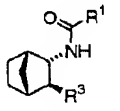
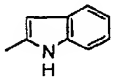
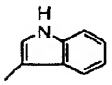
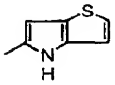
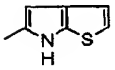
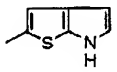
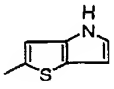
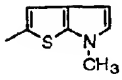
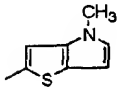
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-61	Ib-61	Ic-61	Id-61	Ie-61	If-61
	Ia-62	Ib-62	Ic-62	Id-62	Ie-62	If-62
	Ia-63	Ib-63	Ic-63	Id-63	Ie-63	If-63
	Ia-64	Ib-64	Ic-64	Id-64	Ie-64	If-64
	Ia-65	Ia-65	Ic-65	Id-65	Ie-65	If-65
	Ia-66	Ib-66	Ic-66	Id-66	Ie-66	If-66
	Ia-67	Ib-67	Ic-67	Id-67	Ie-67	If-67
	Ia-68	Ib-68	Ic-68	Id-68	Ie-68	If-68
	Ia-69	Ib-69	Ic-69	Id-69	Ie-69	If-69
	Ia-70	Ib-70	Ic-70	Id-70	Ie-70	If-70

Table 8

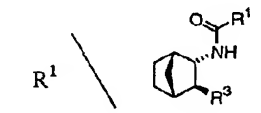
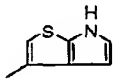
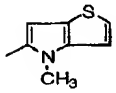
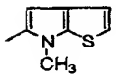
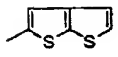
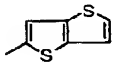
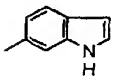
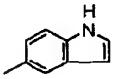
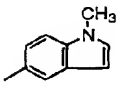
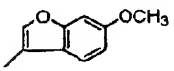
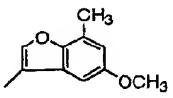
	Ia	Ib	Ic	Id	Ie	If
	Ia-71	Ib-71	Ic-71	Id-71	Ie-71	If-71
	Ia-72	Ib-72	Ic-72	Id-72	Ie-72	If-72
	Ia-73	Ib-73	Ic-73	Id-73	Ie-73	If-73
	Ia-74	Ib-74	Ic-74	Id-74	Ie-74	If-74
	Ia-75	Ia-75	Ic-75	Id-75	Ie-75	If-75
	Ia-76	Ib-76	Ic-76	Id-76	Ie-76	If-76
	Ia-77	Ib-77	Ic-77	Id-77	Ie-77	If-77
	Ia-78	Ib-78	Ic-78	Id-78	Ie-78	If-78
	Ia-79	Ib-79	Ic-79	Id-79	Ie-79	If-79
	Ia-80	Ib-80	Ic-80	Id-80	Ie-80	If-80

Table 9

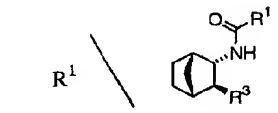
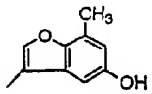
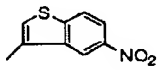
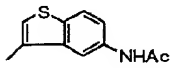
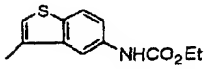
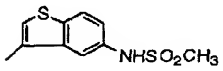
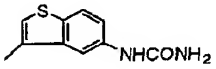
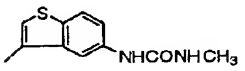
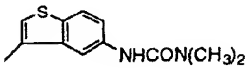
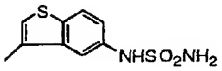
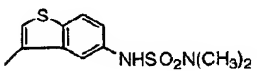
	Ia	Ib	Ic	Id	Ie	If
	Ia-81	Ib-81	Ic-81	Id-81	Ie-81	If-81
	Ia-82	Ib-82	Ic-82	Id-82	Ie-82	If-82
	Ia-83	Ib-83	Ic-83	Id-83	Ie-83	If-83
	Ia-84	Ib-84	Ic-84	Id-84	Ie-84	If-84
	Ia-85	Ib-85	Ic-85	Id-85	Ie-85	If-85
	Ia-86	Ib-86	Ic-86	Id-86	Ie-86	If-86
	Ia-87	Ib-87	Ic-87	Id-87	Ie-87	If-87
	Ia-88	Ib-88	Ic-88	Id-88	Ie-88	If-88
	Ia-89	Ib-89	Ic-89	Id-89	Ie-89	If-89
	Ia-90	Ib-90	Ic-90	Id-90	Ie-90	If-90

Table 10

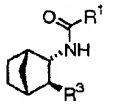
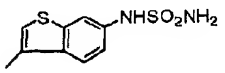
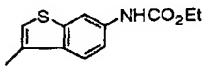
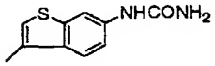
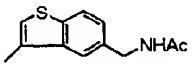
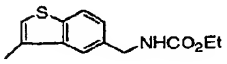
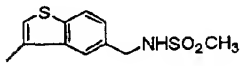
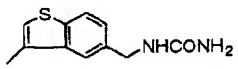
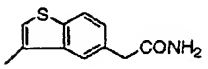
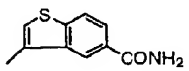
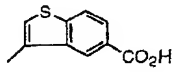
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-91	Ib-91	Ic-91	Id-91	Ie-91	If-91
	Ia-92	Ib-92	Ic-92	Id-92	Ie-92	If-92
	Ia-93	Ib-93	Ic-93	Id-93	Ie-93	If-93
	Ia-94	Ib-94	Ic-94	Id-94	Ie-94	If-94
	Ia-95	Ib-95	Ic-95	Id-95	Ie-95	If-95
	Ia-96	Ib-96	Ic-96	Id-96	Ie-96	If-96
	Ia-97	Ib-97	Ic-97	Id-97	Ie-97	If-97
	Ia-98	Ib-98	Ic-98	Id-98	Ie-98	If-98
	Ia-99	Ib-99	Ic-99	Id-99	Ie-99	If-99
	Ia-100	Ib-100	Ic-100	Id-100	Ie-100	If-100

Table 11

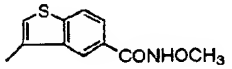
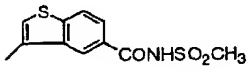
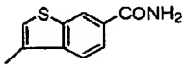
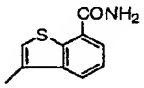
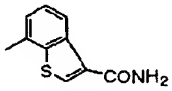
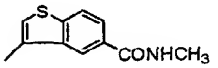
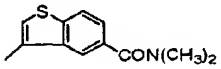
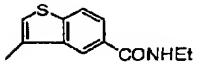
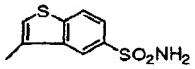
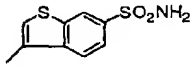
	Ia	Ib	Ic	Id	Ie	If
	Ia-101	Ib-101	Ic-101	Id-101	Ie-101	If-101
	Ia-102	Ib-102	Ic-102	Id-102	Ie-102	If-102
	Ia-103	Ib-103	Ic-103	Id-103	Ie-103	If-103
	Ia-104	Ib-104	Ic-104	Id-104	Ie-104	If-104
	Ia-105	Ib-105	Ic-105	Id-105	Ie-105	If-105
	Ia-106	Ib-106	Ic-106	Id-106	Ie-106	If-106
	Ia-107	Ib-107	Ic-107	Id-107	Ie-107	If-107
	Ia-108	Ib-108	Ic-108	Id-108	Ie-108	If-108
	Ia-109	Ib-109	Ic-109	Id-109	Ie-109	If-109
	Ia-110	Ib-110	Ic-110	Id-110	Ie-110	If-110

Table 12

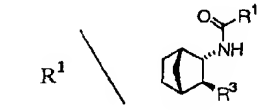
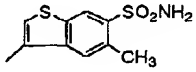
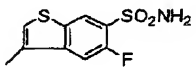
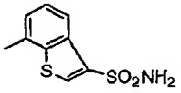
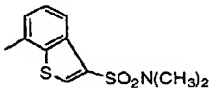
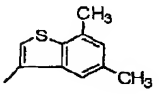
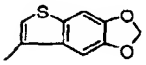
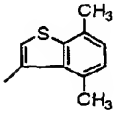
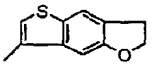
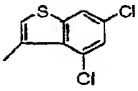
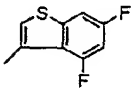
	Ia	Ib	Ic	Id	Ie	If
	Ia-111	Ib-111	Ic-111	Id-111	Ie-111	If-111
	Ia-112	Ib-112	Ic-112	Id-112	Ie-112	If-112
	Ia-113	Ib-113	Ic-113	Id-113	Ie-113	If-113
	Ia-114	Ib-114	Ic-114	Id-114	Ie-114	If-114
	Ia-115	Ib-115	Ic-115	Id-115	Ie-115	If-115
	Ia-116	Ib-116	Ic-116	Id-116	Ie-116	If-116
	Ia-117	Ib-117	Ic-117	Id-117	Ie-117	If-117
	Ia-118	Ib-118	Ic-118	Id-118	Ie-118	If-118
	Ia-119	Ib-119	Ic-119	Id-119	Ie-119	If-119
	Ia-120	Ib-120	Ic-120	Id-120	Ie-120	If-120

Table 13

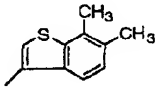
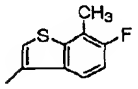
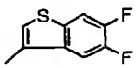
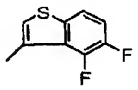
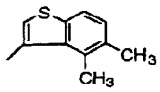
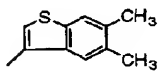
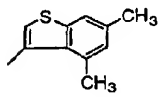
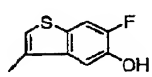
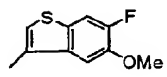
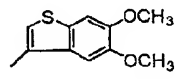
R^1	Ia	Ib	Ic	Id	Ie	If
	Ia-121	Ib-121	Ic-121	Id-121	Ie-121	If-121
	Ia-122	Ib-122	Ic-122	Id-122	Ie-122	If-122
	Ia-123	Ib-123	Ic-123	Id-123	Ie-123	If-123
	Ia-124	Ib-124	Ic-124	Id-124	Ie-124	If-124
	Ia-125	Ib-125	Ic-125	Id-125	Ie-125	If-125
	Ia-126	Ib-126	Ic-126	Id-126	Ie-126	If-126
	Ia-127	Ib-127	Ic-127	Id-127	Ie-127	If-127
	Ia-128	Ib-128	Ic-128	Id-128	Ie-128	If-128
	Ia-129	Ib-129	Ic-129	Id-129	Ie-129	If-129
	Ia-130	Ib-130	Ic-130	Id-130	Ie-130	If-130

Table 14

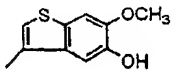
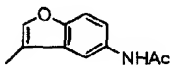
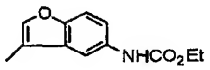
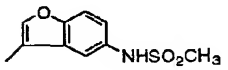
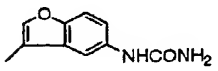
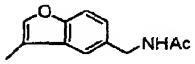
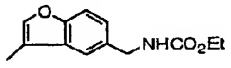
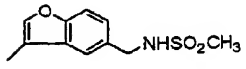
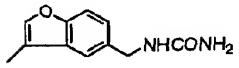
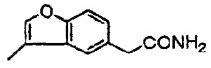
R^1	Ia	Ib	Ic	Id	Ie	If
	Ia-131	Ib-131	Ic-131	Id-131	Ie-131	If-131
	Ia-132	Ib-132	Ic-132	Id-132	Ie-132	If-132
	Ia-133	Ib-133	Ic-133	Id-133	Ie-133	If-133
	Ia-134	Ib-134	Ic-134	Id-134	Ie-134	If-134
	Ia-135	Ib-135	Ic-135	Id-135	Ie-135	If-135
	Ia-136	Ib-136	Ic-136	Id-136	Ie-136	If-136
	Ia-137	Ib-137	Ic-137	Id-137	Ie-137	If-137
	Ia-138	Ib-138	Ic-138	Id-138	Ie-138	If-138
	Ia-139	Ib-139	Ic-139	Id-139	Ie-139	If-139
	Ia-140	Ib-140	Ic-140	Id-140	Ie-140	If-140

Table 15

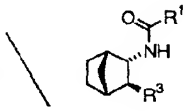
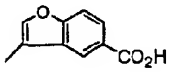
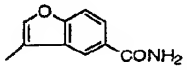
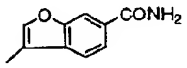
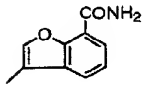
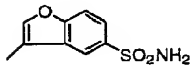
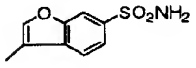
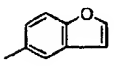
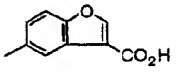
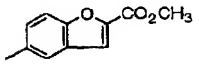
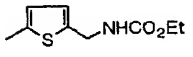
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-141	Ib-141	Ic-141	Id-141	Ie-141	If-141
	Ia-142	Ib-142	Ic-142	Id-142	Ie-142	If-142
	Ia-143	Ib-143	Ic-143	Id-143	Ie-143	If-143
	Ia-144	Ib-144	Ic-144	Id-144	Ie-144	If-144
	Ia-145	Ib-145	Ic-145	Id-145	Ie-145	If-145
	Ia-146	Ib-146	Ic-146	Id-146	Ie-146	If-146
	Ia-147	Ib-147	Ic-147	Id-147	Ie-147	If-147
	Ia-148	Ib-148	Ic-148	Id-148	Ie-148	If-148
	Ia-149	Ib-149	Ic-149	Id-149	Ie-149	If-149
	Ia-150	Ib-150	Ic-150	Id-150	Ie-150	If-150

Table 16

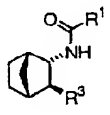
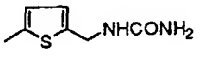
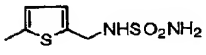
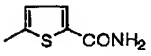
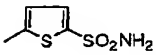
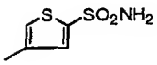
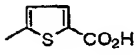
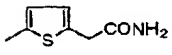
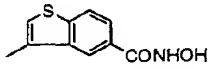
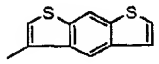
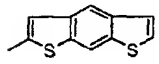
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-151	Ib-151	Ic-151	Id-151	Ie-151	If-151
	Ia-152	Ib-152	Ic-152	Id-152	Ie-152	If-152
	Ia-153	Ib-153	Ic-153	Id-153	Ie-153	If-153
	Ia-154	Ib-154	Ic-154	Id-154	Ie-154	If-154
	Ia-155	Ib-155	Ic-155	Id-155	Ie-155	If-155
	Ia-156	Ib-156	Ic-156	Id-156	Ie-156	If-156
	Ia-157	Ib-157	Ic-157	Id-157	Ie-157	If-157
	Ia-158	Ib-158	Ic-158	Id-158	Ie-158	If-158
	Ia-159	Ib-159	Ic-159	Id-159	Ie-159	If-159
	Ia-160	Ib-160	Ic-160	Id-160	Ie-160	If-160

Table 17

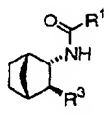
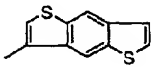
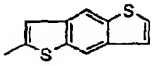
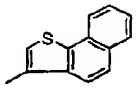
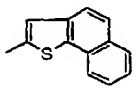
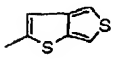
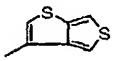
R^1 	Ia	Ib	Ic	Id	Ie	If
	Ia-161	Ib-161	Ic-161	Id-161	Ie-161	If-161
	Ia-162	Ib-162	Ic-162	Id-162	Ie-162	If-162
	Ia-163	Ib-163	Ic-163	Id-163	Ie-163	If-163
	Ia-164	Ib-164	Ic-164	Id-164	Ie-164	If-164
	Ia-165	Ib-165	Ic-165	Id-165	Ie-165	If-165
	Ia-166	Ib-166	Ic-166	Id-166	Ie-166	If-166

Table 18

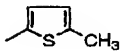
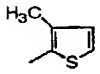
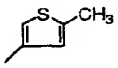
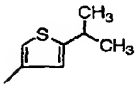
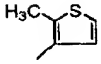
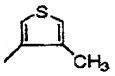
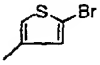
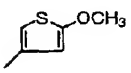
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-1	IIb-1	IIc-1	IId-1	IIe-1	IIf-1
	IIa-2	IIb-2	IIc-2	IId-2	IIe-2	IIf-2
	IIa-3	IIb-3	IIc-3	IId-3	IIe-3	IIf-3
	IIa-4	IIb-4	IIc-4	IId-4	IIe-4	IIf-4
	IIa-5	IIb-5	IIc-5	IId-5	IIe-5	IIf-5
	IIa-6	IIb-6	IIc-6	IId-6	IIe-6	IIf-6
	IIa-7	IIb-7	IIc-7	IId-7	IIe-7	IIf-7
	IIa-8	IIb-8	IIc-8	IId-8	IIe-8	IIf-8
	IIa-9	IIb-9	IIc-9	IId-9	IIe-9	IIf-9
	IIa-10	IIb-10	IIc-10	IId-10	IIe-10	IIf-10

Table 19

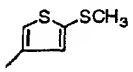
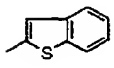
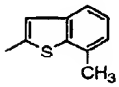
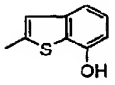
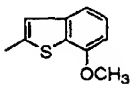
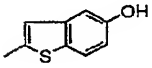
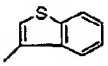
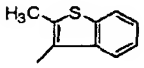
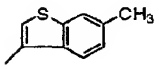
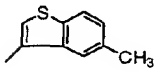
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-11	IIb-11	IIc-11	IId-11	IIe-11	IIf-11
	IIa-12	IIb-12	IIc-12	IId-12	IIe-12	IIf-12
	IIa-13	IIb-13	IIc-13	IId-13	IIe-13	IIf-13
	IIa-14	IIb-14	IIc-14	IId-14	IIe-14	IIf-14
	IIa-15	IIb-15	IIc-15	IId-15	IIe-15	IIf-15
	IIa-16	IIb-16	IIc-16	IId-16	IIe-16	IIf-16
	IIa-17	IIb-17	IIc-17	IId-17	IIe-17	IIf-17
	IIa-18	IIb-18	IIc-18	IId-18	IIe-18	IIf-18
	IIa-19	IIb-19	IIc-19	IId-19	IIe-19	IIf-19
	IIa-20	IIb-20	IIc-20	IId-20	IIe-20	IIf-20

Table 20

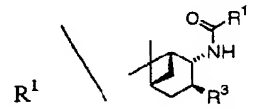
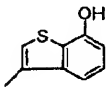
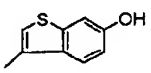
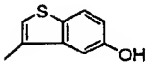
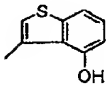
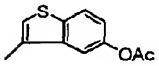
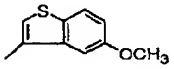
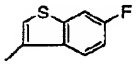
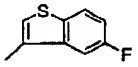
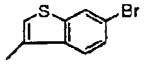
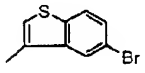
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-21	IIb-21	IIc-21	IId-21	IIe-21	IIf-21
	IIa-22	IIb-22	IIc-22	IId-22	IIe-22	IIf-22
	IIa-23	IIb-23	IIc-23	IId-23	IIe-23	IIf-23
	IIa-24	IIb-24	IIc-24	IId-24	IIe-24	IIf-24
	IIa-25	IIb-25	IIc-25	IId-25	IIe-25	IIf-25
	IIa-26	IIb-26	IIc-26	IId-26	IIe-26	IIf-26
	IIa-27	IIb-27	IIc-27	IId-27	IIe-27	IIf-27
	IIa-28	IIb-28	IIc-28	IId-28	IIe-28	IIf-28
	IIa-29	IIb-29	IIc-29	IId-29	IIe-29	IIf-29
	IIa-30	IIb-30	IIc-30	IId-30	IIe-30	IIf-30

Table 21

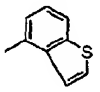
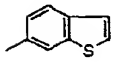
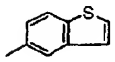
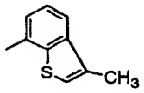
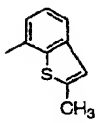
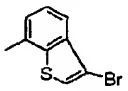
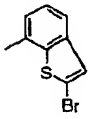
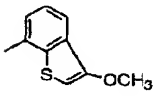
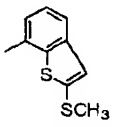
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-31	IIb-31	IIc-31	IId-31	IIe-31	IIf-31
	IIa-32	IIb-32	IIc-32	IId-32	IIe-32	IIf-32
	IIa-33	IIb-33	IIc-33	IId-33	IIe-33	IIf-33
	IIa-34	IIb-34	IIc-34	IId-34	IIe-34	IIf-34
	IIa-35	IIb-35	IIc-35	IId-35	IIe-35	IIf-35
	IIa-36	IIb-36	IIc-36	IId-36	IIe-36	IIf-36
	IIa-37	IIb-37	IIc-37	IId-37	IIe-37	IIf-37
	IIa-38	IIb-38	IIc-38	IId-38	IIe-38	IIf-38
	IIa-39	IIb-39	IIc-39	IId-39	IIe-39	IIf-39
	IIa-40	IIb-40	IIc-40	IId-40	IIe-40	IIf-40

Table 22

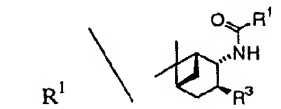
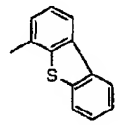
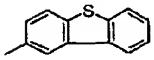
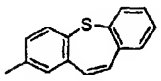
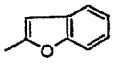
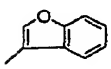
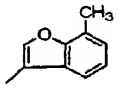
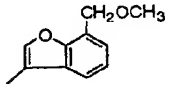
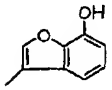
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-41	IIb-41	IIc-41	IId-41	IIe-41	IIf-41
	IIa-42	IIb-42	IIc-42	IId-42	IIe-42	IIf-42
	IIa-43	IIb-43	IIc-43	IId-43	IIe-43	IIf-43
	IIa-44	IIb-44	IIc-44	IId-44	IIe-44	IIf-44
	IIa-45	IIb-45	IIc-45	IId-45	IIe-45	IIf-45
	IIa-46	IIb-46	IIc-46	IId-46	IIe-46	IIf-46
	IIa-47	IIb-47	IIc-47	IId-47	IIe-47	IIf-47
	IIa-48	IIb-48	IIc-48	IId-48	IIe-48	IIf-48
	IIa-49	IIb-49	IIc-49	IId-49	IIe-49	IIf-49
	IIa-50	IIb-50	IIc-50	IId-50	IIe-50	IIf-50

Table 23

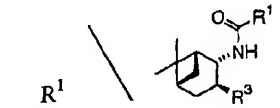
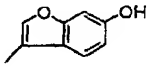
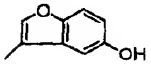
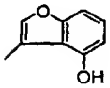
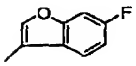
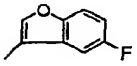
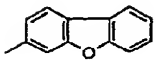
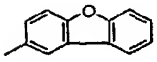
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-51	IIb-51	IIc-51	IId-51	IIe-51	IIf-51
	IIa-52	IIb-52	IIc-52	IId-52	IIe-52	IIf-52
	IIa-53	IIb-53	IIc-53	IId-53	IIe-53	IIf-53
	IIa-54	IIb-54	IIc-54	IId-54	IIe-54	IIf-54
	IIa-55	IIb-55	IIc-55	IId-55	IIe-55	IIf-55
	IIa-56	IIb-56	IIc-56	IId-56	IIe-56	IIf-56
	IIa-57	IIb-57	IIc-57	IId-57	IIe-57	IIf-57
	IIa-58	IIb-58	IIc-58	IId-58	IIe-58	IIf-58
	IIa-59	IIb-59	IIc-59	IId-59	IIe-59	IIf-59
	IIa-60	IIb-60	IIc-60	IId-60	IIe-60	IIf-60

Table 24

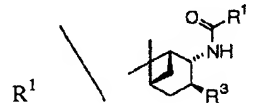
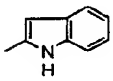
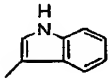
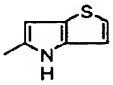
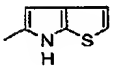
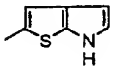
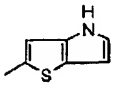
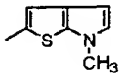
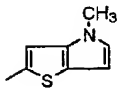
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-61	IIb-61	IIc-61	IId-61	IIe-61	IIf-61
	IIa-62	IIb-62	IIc-62	IId-62	IIe-62	IIf-62
	IIa-63	IIb-63	IIc-63	IId-63	IIe-63	IIf-63
	IIa-64	IIb-64	IIc-64	IId-64	IIe-64	IIf-64
	IIa-65	IIb-65	IIc-65	IId-65	IIe-65	IIf-65
	IIa-66	IIb-66	IIc-66	IId-66	IIe-66	IIf-66
	IIa-67	IIb-67	IIc-67	IId-67	IIe-67	IIf-67
	IIa-68	IIb-68	IIc-68	IId-68	IIe-68	IIf-68
	IIa-69	IIb-69	IIc-69	IId-69	IIe-69	IIf-69
	IIa-70	IIb-70	IIc-70	IId-70	IIe-70	IIf-70

Table 25

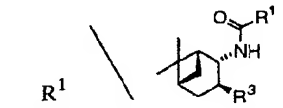
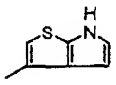
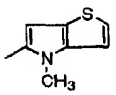
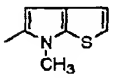
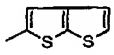
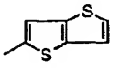
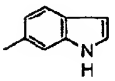
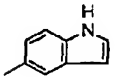
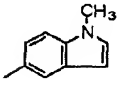
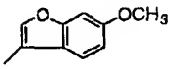
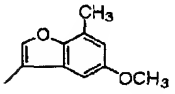
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-71	IIb-71	IIc-71	IId-71	IIe-71	IIf-71
	IIa-72	IIb-72	IIc-72	IId-72	IIe-72	IIf-72
	IIa-73	IIb-73	IIc-73	IId-73	IIe-73	IIf-73
	IIa-74	IIb-74	IIc-74	IId-74	IIe-74	IIf-74
	IIa-75	IIb-75	IIc-75	IId-75	IIe-75	IIf-75
	IIa-76	IIb-76	IIc-76	IId-76	IIe-76	IIf-76
	IIa-77	IIb-77	IIc-77	IId-77	IIe-77	IIf-77
	IIa-78	IIb-78	IIc-78	IId-78	IIe-78	IIf-78
	IIa-79	IIb-79	IIc-79	IId-79	IIe-79	IIf-79
	IIa-80	IIb-80	IIc-80	IId-80	IIe-80	IIf-80

Table 26

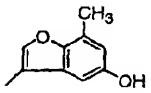
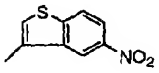
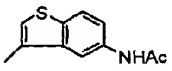
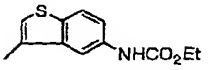
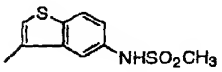
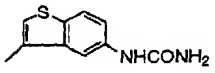
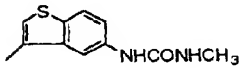
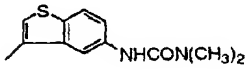
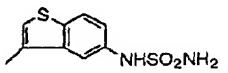
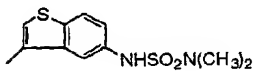
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-81	IIb-81	IIc-81	IId-81	IIe-81	IIf-81
	IIa-82	IIb-82	IIc-82	IId-82	IIe-82	IIf-82
	IIa-83	IIb-83	IIc-83	IId-83	IIe-83	IIf-83
	IIa-84	IIb-84	IIc-84	IId-84	IIe-84	IIf-84
	IIa-85	IIb-85	IIc-85	IId-85	IIe-85	IIf-85
	IIa-86	IIb-86	IIc-86	IId-86	IIe-86	IIf-86
	IIa-87	IIb-87	IIc-87	IId-87	IIe-87	IIf-87
	IIa-88	IIb-88	IIc-88	IId-88	IIe-88	IIf-88
	IIa-89	IIb-89	IIc-89	IId-89	IIe-89	IIf-89
	IIa-90	IIb-90	IIc-90	IId-90	IIe-90	IIf-90

Table 27

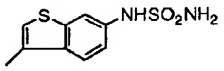
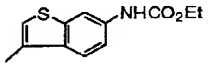
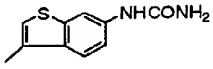
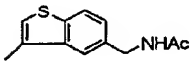
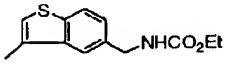
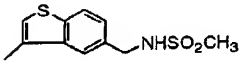
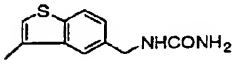
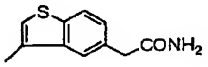
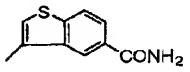
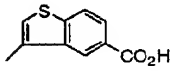
R^1	IIa	IIb	IIc	IId	IIe	IIf
	IIa-91	IIb-91	IIc-91	IId-91	IIe-91	IIf-91
	IIa-92	IIb-92	IIc-92	IId-92	IIe-92	IIf-92
	IIa-93	IIb-93	IIc-93	IId-93	IIe-93	IIf-93
	IIa-94	IIb-94	IIc-94	IId-94	IIe-94	IIf-94
	IIa-95	IIb-95	IIc-95	IId-95	IIe-95	IIf-95
	IIa-96	IIb-96	IIc-96	IId-96	IIe-96	IIf-96
	IIa-97	IIb-97	IIc-97	IId-97	IIe-97	IIf-97
	IIa-98	IIb-98	IIc-98	IId-98	IIe-98	IIf-98
	IIa-99	IIb-99	IIc-99	IId-99	IIe-99	IIf-99
	IIa-100	IIb-100	IIc-100	IId-100	IIe-100	IIf-100

Table 28

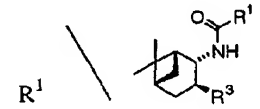
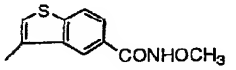
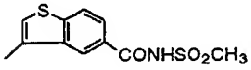
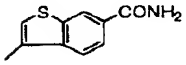
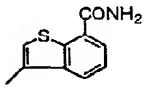
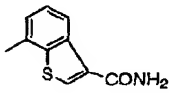
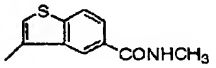
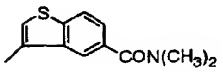
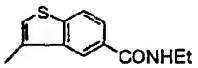
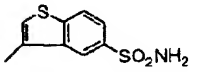
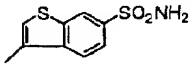
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-101	IIb-101	IIc-101	IId-101	IIe-101	IIf-101
	IIa-102	IIb-102	IIc-102	IId-102	IIe-102	IIf-102
	IIa-103	IIb-103	IIc-103	IId-103	IIe-103	IIf-103
	IIa-104	IIb-104	IIc-104	IId-104	IIe-104	IIf-104
	IIa-105	IIb-105	IIc-105	IId-105	IIe-105	IIf-105
	IIa-106	IIb-106	IIc-106	IId-106	IIe-106	IIf-106
	IIa-107	IIb-107	IIc-107	IId-107	IIe-107	IIf-107
	IIa-108	IIb-108	IIc-108	IId-108	IIe-108	IIf-108
	IIa-109	IIb-109	IIc-109	IId-109	IIe-109	IIf-109
	IIa-110	IIb-110	IIc-110	IId-110	IIe-110	IIf-110

Table 29

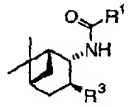
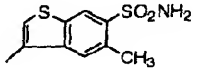
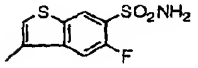
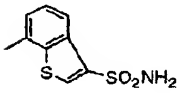
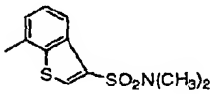
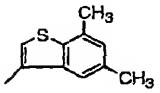
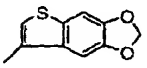
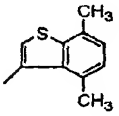
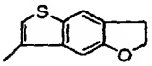
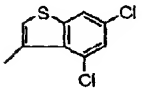
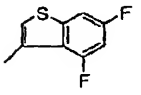
R^1 	IIa	IIb	IIc	IId	IIe	IIf
	IIa-111	IIb-111	IIc-111	IId-111	IIe-111	IIf-111
	IIa-112	IIb-112	IIc-112	IId-112	IIe-112	IIf-112
	IIa-113	IIb-113	IIc-113	IId-113	IIe-113	IIf-113
	IIa-114	IIb-114	IIc-114	IId-114	IIe-114	IIf-114
	IIa-115	IIb-115	IIc-115	IId-115	IIe-115	IIf-115
	IIa-116	IIb-116	IIc-116	IId-116	IIe-116	IIf-116
	IIa-117	IIb-117	IIc-117	IId-117	IIe-117	IIf-117
	IIa-118	IIb-118	IIc-118	IId-118	IIe-118	IIf-118
	IIa-119	IIb-119	IIc-119	IId-119	IIe-119	IIf-119
	IIa-120	IIb-120	IIc-120	IId-120	IIe-120	IIf-120

Table 30

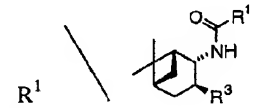
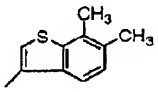
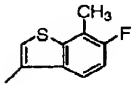
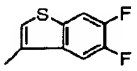
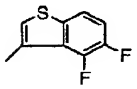
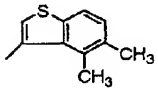
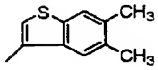
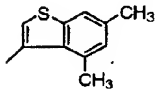
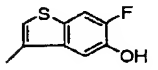
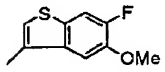
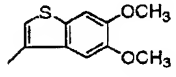
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-121	IIb-121	IIc-121	IId-121	IIe-121	IIf-121
	IIa-122	IIb-122	IIc-122	IId-122	IIe-122	IIf-122
	IIa-123	IIb-123	IIc-123	IId-123	IIe-123	IIf-123
	IIa-124	IIb-124	IIc-124	IId-124	IIe-124	IIf-124
	IIa-125	IIb-125	IIc-125	IId-125	IIe-125	IIf-125
	IIa-126	IIb-126	IIc-126	IId-126	IIe-126	IIf-126
	IIa-127	IIb-127	IIc-127	IId-127	IIe-127	IIf-127
	IIa-128	IIb-128	IIc-128	IId-128	IIe-128	IIf-128
	IIa-129	IIb-129	IIc-129	IId-129	IIe-129	IIf-129
	IIa-130	IIb-130	IIc-130	IId-130	IIe-130	IIf-130

Table 31

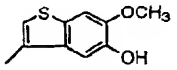
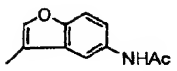
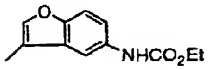
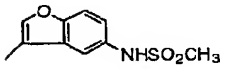
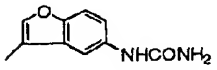
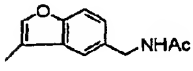
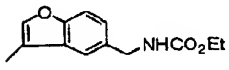
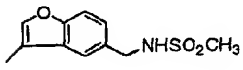
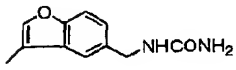
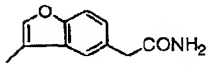
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-131	IIb-131	IIc-131	IId-131	IIe-131	IIf-131
	IIa-132	IIb-132	IIc-132	IId-132	IIe-132	IIf-132
	IIa-133	IIb-133	IIc-133	IId-133	IIe-133	IIf-133
	IIa-134	IIb-134	IIc-134	IId-134	IIe-134	IIf-134
	IIa-135	IIb-135	IIc-135	IId-135	IIe-135	IIf-135
	IIa-136	IIb-136	IIc-136	IId-136	IIe-136	IIf-136
	IIa-137	IIb-137	IIc-137	IId-137	IIe-137	IIf-137
	IIa-138	IIb-138	IIc-138	IId-138	IIe-138	IIf-138
	IIa-139	IIb-139	IIc-139	IId-139	IIe-139	IIf-139
	IIa-140	IIb-140	IIc-140	IId-140	IIe-140	IIf-140

Table 32

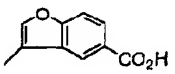
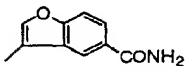
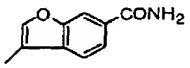
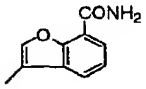
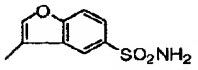
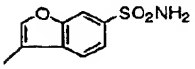
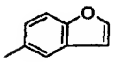
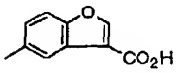
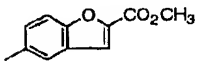
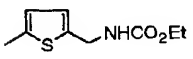
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-141	IIb-141	IIc-141	IId-141	IIe-141	IIf-141
	IIa-142	IIb-142	IIc-142	IId-142	IIe-142	IIf-142
	IIa-143	IIb-143	IIc-143	IId-143	IIe-143	IIf-143
	IIa-144	IIb-144	IIc-144	IId-144	IIe-144	IIf-144
	IIa-145	IIb-145	IIc-145	IId-145	IIe-145	IIf-145
	IIa-146	IIb-146	IIc-146	IId-146	IIe-146	IIf-146
	IIa-147	IIb-147	IIc-147	IId-147	IIe-147	IIf-147
	IIa-148	IIb-148	IIc-148	IId-148	IIe-148	IIf-148
	IIa-149	IIb-149	IIc-149	IId-149	IIe-149	IIf-149
	IIa-150	IIb-150	IIc-150	IId-150	IIe-150	IIf-150

Table 33

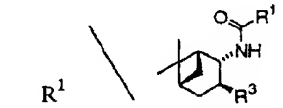
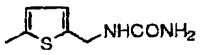
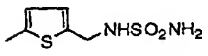
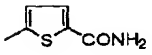
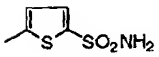
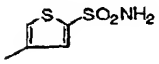
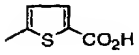
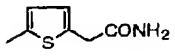
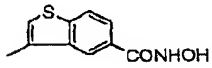
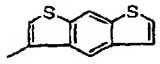
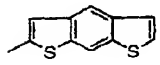
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-151	IIb-151	IIc-151	IId-151	IIe-151	IIf-151
	IIa-152	IIb-152	IIc-152	IId-152	IIe-152	IIf-152
	IIa-153	IIb-153	IIc-153	IId-153	IIe-153	IIf-153
	IIa-154	IIb-154	IIc-154	IId-154	IIe-154	IIf-154
	IIa-155	IIb-155	IIc-155	IId-155	IIe-155	IIf-155
	IIa-156	IIb-156	IIc-156	IId-156	IIe-156	IIf-156
	IIa-157	IIb-157	IIc-157	IId-157	IIe-157	IIf-157
	IIa-158	IIb-158	IIc-158	IId-158	IIe-158	IIf-158
	IIa-159	IIb-159	IIc-159	IId-159	IIe-159	IIf-159
	IIa-160	IIb-160	IIc-160	IId-160	IIe-160	IIf-160

Table 34

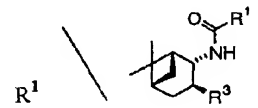
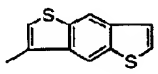
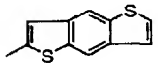
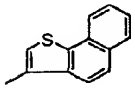
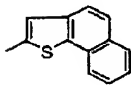
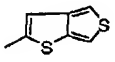
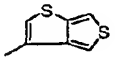
	IIa	IIb	IIc	IId	IIe	IIf
	IIa-161	IIb-161	IIc-161	IId-161	IIe-161	IIf-161
	IIa-162	IIb-162	IIc-162	IId-162	IIe-162	IIf-162
	IIa-163	IIb-163	IIc-163	IId-163	IIe-163	IIf-163
	IIa-164	IIb-164	IIc-164	IId-164	IIe-164	IIf-164
	IIa-165	IIb-165	IIc-165	IId-165	IIe-165	IIf-165
	IIa-166	IIb-166	IIc-166	IId-166	IIe-166	IIf-166

Table 35

Compound No.	Physical property
Ia-04	mp 175-178 °C; ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.04 (1H, m), 1.25-1.49 (10H, m), 1.57-1.66 (2H, m), 2.00 (1H, m), 2.15-2.22 (2H, m), 2.51 (1H, m), 3.82 (1H, m), 5.77 (1H, dt, J = 15.9, 1.5 Hz), 6.41 (1H, d, J = 7.8 Hz), 6.95 (1H, dt, J = 15.9, 7.1 Hz), 7.34 (1H, dd, J = 3.0, 4.8 Hz), 7.41 (1H, dd, J = 1.5, 4.8 Hz), 7.90 (1H, dd, J = 1.5, 3.0 Hz); IR (Nujol) 3363, 3105, 2627, 1697, 1618, 1554, 1248 cm^{-1}; $[\alpha]_D^{25}$+44.3±0.8° (c=1.011, MeOH); Anal. ($C_{19}H_{25}NO_3S$) Calcd. (%): C, 65.68; H, 7.25; N, 4.03; S, 9.23 Found (%): C, 65.58; H, 7.18; N, 4.03; S, 9.18
Ia-17	mp 155-157 °C; ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.04 (1H, m), 1.22-1.53 (10H, m), 1.60-1.71 (2H, m), 2.02 (1H, m), 2.17-2.23 (2H, m), 2.58 (1H, m), 3.92 (1H, m), 5.78 (1H, dt, J = 15.6, 1.5 Hz), 6.33 (1H, d, J = 7.5 Hz), 6.97 (1H, dt, J = 15.6, 6.9 Hz), 7.38-7.49 (2H, m), 7.86-7.89 (3H, m), 8.30 (1H, dd, J = 0.9, 6.9 Hz); IR (Nujol) 3276, 2671, 1693, 1622, 1529, 1421, 1377, 1298, 1277, 1254 cm^{-1}; $[\alpha]_D^{25}$ +38.5±0.8° (c=1.018, MeOH); Anal. ($C_{23}H_{27}NO_3S \cdot 0.2H_2O$) Calcd. (%): C, 68.87; H, 6.88; N, 3.49; S, 7.99 Found (%): C, 68.93; H, 7.01; N, 3.55; S, 7.87
Ia-20	mp 129-131 °C; ^{1}H-NMR ($CDCl_3$) δ 1.01 (1H, m), 1.26-1.52 (10H, m), 1.60-1.66 (2H, m), 2.02 (1H, m), 2.18-2.25 (2H, m), 2.49 (3H, s), 2.58 (1H, m), 3.95 (1H, m), 5.80 (1H, d, J = 15.6 Hz), 6.06 (1H, d, J = 7.8 Hz), 7.04 (1H, dt, J = 15.6, 7.1 Hz), 7.23 (1H, dd, J = 1.2, 8.4 Hz), 7.74 (1H, d, J = 8.4 Hz), 7.80 (1H, s), 8.14 (1H, s); IR (Nujol) 3269, 3078, 2677, 1697, 1649, 1624, 1539, 1437, 1377, 1298, 1281 cm^{-1}; $[\alpha]_D^{25}$ +32.0±0.7° (c=1.005, MeOH); Anal. ($C_{24}H_{29}NO_3S$) Calcd. (%): C, 70.04; H, 7.10; N, 3.40; S, 7.79 Found (%): C, 69.83; H, 7.10; N, 3.43; S, 7.64
Ia-28	mp 138-140 °C; ^{1}H-NMR ($CDCl_3$) δ 1.02 (1H, m), 1.21-1.52 (10H, m), 1.59-1.70 (2H, m), 2.01 (1H, m), 2.17-2.24 (2H, m), 2.56 (1H, m), 3.92 (1H, m), 5.79 (1H, dt, J = 15.6, 1.5 Hz), 6.14 (1H, d, J = 8.1 Hz), 7.03 (1H, dt, J = 15.6, 7.1 Hz), 7.16 (1H, td, J = 8.6, 2.7 Hz), 7.77 (1H, dd, J = 4.8, 8.6 Hz), 7.91 (1H, s), 8.07 (1H, dd, J = 2.7, 10.2 Hz); IR (Nujol) 3276, 2671, 1695, 1624, 1533, 1442, 1433, 1296, 1277, 1246, 1200 cm^{-1}; $[\alpha]_D^{25}$ +35.6±0.8° (c=1.014, MeOH); Anal. ($C_{23}H_{26}FNO_3S \cdot 0.2H_2O$) Calcd. (%): C, 65.91; H, 6.35; F,4.53; N, 3.34; S, 7.65 Found (%): C, 65.99; H, 6.38; F,4.42; N, 3.39; S, 7.57
Ia-34	mp 172-173 °C; ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.08 (1H, m), 1.29-1.55 (10H, m), 1.60-1.69 (2H, m), 2.03 (1H, m), 2.14-2.21 (2H, m), 2.60 (1H, m), 3.96 (1H, m), 5.76 (1H, dt, J = 15.6,1.5 Hz), 6.57 (1H, d, J = 7.5-Hz), 6.97 (1H, dt, J = 15.6, 7.1 Hz), 7.38 (1H, d, J = 5.7 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.59 (1H, d, J = 5.7 Hz), 7.65 (1H, d, J = 6.9 Hz), 7.95 (1H, d, J = 7.8 Hz); IR (Nujol) 3302, 2698, 1739, 1693, 1657, 1622, 1581, 1568, 1547, 1205 cm^{-1}; $[\alpha]_D^{25}$ +35.0±0.7° (c=1.013, MeOH); Anal. ($C_{23}H_{27}NO_3S \cdot 0.2H_2O$) Calcd. (%): C, 68.87; H, 6.88; N, 3.49; S, 7.99 Found (%): C, 68.92; H, 7.05; N, 3.44; S, 7.67

Table 36

Compound No.	Physical property
Ia-49	^{1}H-NMR ($CDCl_3$) δ 1.02 (1H, m), 1.29-1.74 (12H, m), 2.02 (1H, m), 2.17-2.24 (2H, m), 2.56 (1H, m), 3.44 (3H, s), 3.96 (1H, m), 4.79 (2H, s), 5.79 (1H, dt, J = 15.6, 1.2 Hz), 5.98 (1H, d, J = 7.8 Hz), 7.01 (1H, dt, J = 15.6, 7.2 Hz), 7.33-7.40 (2H, m), 7.77 (1H, dd, J = 7.2, 2.4 Hz), 8.14 (1H, s) ; IR ($CHCl_3$) 3442, 2682, 1695, 1652, 1573, 1508, 1425, 1284, 1205, 1120 cm^{-1}; $[\alpha]_D^{25.0}$ +31.0±0.7° (c=1.009, MeOH); Anal. ($C_{25}H_{31}NO_5 \cdot 0.5H_2O$) Calcd. (%): C, 69.10; H, 7.42; N, 3.22 Found (%): C, 68.83; H, 7.48; N, 3.30
Ia-51	^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.03 (1H, m), 1.20-1.51 (9H, m), 1.59-1.71 (3H, m), 2.01 (1H, d, J = 3.6 Hz), 2.15-2.22 (2H, m), 2.56 (1H, s), 3.90 (1H, m), 5.77 (1H, d, J = 15.6 Hz), 6.90 (1H, dd, J = 2.1, 8.4 Hz), 6.96 (1H, dt, J = 15.6, 6.9 Hz), 6.99 (1H, d, J = 2.1 Hz) , 7.58 (1H, d, J = 8.4 Hz), 8.01 (1H, s); IR (KBr) 3350, 3141, 1695, 1628, 1560, 1523, 1493, 1441, 1367, 1279, 1225, 1136, 1124 cm^{-1}; $[\alpha]_D^{27}$+26.6±0.7° (c=1.008, MeOH); Anal. ($C_{23}H_{27}NO_5 \cdot 0.3H_2O$) Calcd. (%): C, 68.57; H, 6.91; N, 3.48 Found (%): C, 68.47; H, 6.91; N, 3.66

Table 36 (continued)

Compound No.	Physical property
Ia-52	^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.02 (1H, m), 1.22-1.48 (9H, m), 1.57-1.60 (3H, m), 1.98 (1H, d, J = 3.3 Hz), 2.11-2.18 (2H, m), 2.53 (1H, s), 3.89 (1H, m), 5.75 (1H, dd, J = 1.5, 15.3 Hz), 6.31 (1H, d, J = 7.8 Hz), 6.90 (1H, dd, J = 2.4, 8.7 Hz), 6.96 (1H, dt, J = 15.3, 6.9 Hz), 7.33 (1H, d, J = 8.7 Hz), 7.43 (1H, d, J = 2.4 Hz), 8.07 (1H, s); IR (KBr) 3347, 1695, 1635, 1558, 1524, 1462, 1309, 1271, 1192, 1173, 1134 cm^{-1}; $[\alpha]_D^{25}$+20.1±0.6° (c=1.013, MeOH); Anal. ($C_{23}H_{27}NO_5 \cdot 0.4H_2O$) Calcd. (%): C, 68.27; H, 6.92; N, 3.46 Found (%): C, 68.12; H, 7.00; N, 3.59
Ia-54	^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.23-1.72 (10H, m), 2.02 (1H, m), 2.18-2.25 (2H, m), 2.55 (1H, m), 3.94 (1H, m), 5.79 (1H, dt, J = 15.6, 1.5 Hz), 5.91 (1H, d, J = 8.1 Hz), 7.03 (1H, dt, J = 15.6, 6.9 Hz), 7.09-7.16 (1H, m), 7.25 (1H, dd, J = 9.0, 1.8 Hz), 7.84 (1H, dd, J = 9.0, 5.4 Hz), 8.06 (1H, s); IR ($CHCl_3$) 3442, 2680, 1695, 1652, 1563, 1506, 1257, 1224, 1218, 1133, cm^{-1}; $[\alpha]_D^{25.0}$ +25.4±0.7° (c=1.005, MeOH); Anal. ($C_{23}H_{26}FNO_4 \cdot 0.1H_2O$) Calcd. (%): C, 68.85; H, 6.58; F, 4.73; N, 3.49 Found (%): C, 68.65; H, 6.43; F, 4.59; N, 3.60
Ia-56	^{1}H-NMR ($CDCl_3$) δ 1.12 (1H, m), 1.29-1.53 (9H, m), 1.60.1.74 (3H, m), 2.04 (1H, d, J = 3.6 Hz), 2.16-2.22 (2H, m), 2.57 (1H, s), 4.03 (1H, m), 5.77 (1H, d, J = 15.6 Hz), 6.89 (1H, d, J = 2.1 Hz), 7.02 (1H, dt, J = 15.3, 7.2 Hz), 7.36 (1H, t, J = 7.5 Hz), 7.57 (1H, d, J = 7.8 Hz), 7.74 (1H, dd, J = 1.2, 7.5 Hz), 7.74 (1H, d, J=2.1Hz), 8.11 (1H, dd, J = 1.2, 7.5 Hz); IR ($CHCl_3$) 3435, 2679, 1695, 1653, 1595, 1547, 1533, 1475, 1458, 1421, 1306, 1286, 1167, 1120 cm^{-1}; $[\alpha]_D^{25.5}$+47.7±0.9° (c=1.003, MeOH); Anal. ($C_{23}H_{27}NO_4 \cdot 0.1H_2O$) Calcd. (%): C, 72.08; H, 7.15; N, 3.65Found (%): C, 72.01; H, 7.11; N, 3.72

Table 37

Compound No.	Physical property
Ia-65	^{1}H-NMR ($CDCl_3$) δ 1.02 (1H, m), 1.27-1.71 (12H, m), 2.01 (1H, d, J = 3.9 Hz), 2.16-2.23 (2H, m), 2.48 (1H, br s), 3.92 (1H, m), 5.81 (1H, d, J = 15.6 Hz), 6.08 (1H, d, J = 8.4 Hz), 6.80 (1H, d, J = 1.5 Hz), 6.98 (1H, dt, J = 5.4 and 0.6 Hz), 7.03 (1H, dt, J = 15.6 and 6.9 Hz), 10.49 (1H, s); IR ($CHCl_3$) 3446, 3215, 1726, 1693, 1643, 1541, 1504, 1477, 1462, 1402, 1373, 1303, 1248 cm^{-1}; $[\alpha]_D^{26}$+67.8±1.1° (c=1.002, MeOH) Anal. ($C_{21}H_{26}N_2O_3S \cdot 0.25\ CH_3COOEt$) Calcd. (%): C, 63.43; H, 6.77; N, 6.72; S, 7.69Found (%): C, 63.66; H, 6.60; N, 6.93; S, 7.60
Ia-66	^{1}H-NMR ($CDCl_3$) δ 1.02 (1H, m), 1.27-1.70 (12H, m), 2.01 (1H, d, J = 3.6 Hz), 2.15-2.22 (2H, m), 2.51 (1H, br s), 3.92 (1H, m), 5.80 (1H, d, J = 15.6 Hz), 6.08 (1H, d, J = 7.8 Hz), 6.77 (1H, d, J = 2.1 Hz), 6.88 (1H, d, J = 5.4 Hz), 6.95 (1H, d, J = 5.4 Hz), 7.03 (1H, dt, J = 15.6 and 6.9 Hz), 11.07 (1H, s); IR ($CHCl_3$) 3444, 3191, 2677, 1693, 1639, 1543, 1518, 1475, 1458, 1421, 1396, 1378, 1296, 1279, 1255 cm^{-1}; $[\alpha]_D^{26}$ +55.3±1.0° (c=1.001, MeOH) Anal. ($C_{21}H_{26}N_2O_3S \cdot 0.3H_2O$) Calcd. (%): C, 64.36; H, 6.84; N, 7.15; S, 8.18 Found (%): C, 64.22; H, 6.48; N, 7.13; S, 8.22
Ia-95	mp 113-114 °C; ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ 1.12 (1H, m), 1.26 (3H, t, J = 6.9 Hz), 1.27-1.64 (12H, m), 2.01 (1H, m), 2.15-2.22 (2H, m), 2.57 (1H, br s), 3.90 (1H, m), 4.14 (2H, q, J = 6.9 Hz), 4.48 (2H, br s), 5.57 (1H, br s), 5.77 (1H, d, J = 15.6 Hz), 6.68 (1H, br s), 6.92 (1H, dd, J = 15.6, 7.2 Hz), 7.38 (1H, br d, J = 8.1 Hz), 7.81 (1H, d, J = 8.1 Hz), 7.95 (1H, s), 8.33 (1H, br s); IR ($CHCl_3$) 3446, 1703, 1653, 1514, 1435, 1300, 1223, 1134 cm^{-1}; $[\alpha]_D^{23}$ +5.5±0.5° (c=1.008, MeOH) Anal. ($C_{27}H_{34}N_2O_5S \cdot 0.3H_2O$) Calcd. (%): C, 64.34; H, 6.92; N, 5.56; S, 6.36 Found (%): C, 64.27; H, 6.69; N, 5.54; S, 6.37
Ic-04	mp 105-107 °C; ^{1}H-NMR ($CDCl_3$) δ 1.02 (1H, m), 1.20-1.70 (12H, m), 2.00 (1H, m), 2.49 (1H, br s), 3.47-3.58 (2H, m), 3.91 (1H, m), 4.04 (2H, s), 6.07 (1H, d, J = 7.2 Hz), 7.34 (1H, dd, J = 3.0, 5.1 Hz), 7.37 (1H, dd, J = 1.5, 5.1 Hz), 7.88 (1H, dd, J = 1.5, 3.0 Hz) ; IR (Nujol) 3354, 3093, 2553, 1730, 1612, 1556, 1240, 1138 cm^{-1}; $[\alpha]_D^{25}$ +46.6±0.9° (c=1.009, MeOH); Anal. ($C_{18}H_{25}NO_4S$) Calcd. (%): C, 61.51; H, 7.17; N, 3.99; S, 9.12 Found (%): C, 61.45; H, 7.32; N, 4.06; S, 9.10

Table 37 (continued)

Compound No.	Physical property
Ic-17	mp 149-151 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.21-1.72 (12H, m), 2.02 (1H, m), 2.57 (1H, br s), 3.47-3.58 (2H, m), 3.98 (1H, m), 4.03 (2H, s), 6.14 (1H, d, J = 7.8 Hz), 7.40 (1H, d, J = 7.8 Hz), 7.44 (1H, dt, J = 1.2, 7.5 Hz), 7.46 (1H, dt, J = 1.2, 7.5 Hz), 7.87 (1H, dd, J = 1.2, 7.5 Hz), 7.88 (1H, s), 8.29 (1H, dd, J = 1.2, 7.5 Hz); IR (Nujol) 3296, 2528, 1726, 1604, 1558, 1240, 1228, 1140 cm^{-1}, $[\alpha]_D^{25}$ +38.1±0.8° (c=1.013, MeOH); Anal. ($C_{22}H_{27}NO_4S$) Calcd. (%): C, 65.18; H, 6.78; N, 3.49; S, 7.99 Found (%): C, 65.62; H, 7.06; N, 3.51; S, 7.78

Table 38

Compound No.	Physical property
Ic-19	mp 145-147 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.21-1.33 (2H, m), 1.40-1.71 (10H, m), 2.01 (1H, m), 2.48 (3H, s), 2.56 (1H, br s), 3.47-3.58 (2H, m), 3.97 (1H, m), 4.03 (2H, s), 6.12 (1H, d, J = 7.8 Hz), 7.28 (1H, m), 7.65 (1H, m), 7.78 (1H, s), 8.15 (1H, d, J = 8.4 Hz); IR (Nujol) 3288, 2521, 1724, 1601, 1560, 1225, 1138 cm^{-1}; $[\alpha]_D^{25}$ +36.8±0.8° (c=1.008, MeOH) Anal. ($C_{23}H_{29}NO_4S$) Calcd. (%): C, 66.48; H, 7.03; N, 3.37; S, 7.72 Found (%): C, 66.33; H, 7.03; N, 3.30; S, 7.43
Ic-20	mp 135-136 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.21-1.72 (12H, m), 2.02 (1H, m), 2.49 (3H, s), 2.57 (1H, br s), 3.48-3.59 (2H, m), 3.97(1H, m), 4.03 (2H, s), 6.12 (1H, d, J = 7.5 Hz), 7.23 (1H, dd, J = 1.5, 8.4 Hz), 7.74 (1H, d, J = 8.4 Hz), 7.83 (1H, s), 8.12 (1H, d, J = 1.5 Hz); IR (Nujol) 3384, 3361, 2546, 1736, 1718, 1616, 1533, 1225, 1140 cm^{-1}; $[\alpha]_D^{25}$ +32.4±0.7° (c=1.003, MeOH); Anal. ($C_{23}H_{29}NO_4S$) Calcd. (%): C, 66.48; H, 7.03; N, 3.37; S, 7.72Found (%): C, 66.31; H, 7.32; N, 3.34; S, 7.60
Ic-22	mp 76-79 °C; ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.07 (1H, m), 1.20-1.32 (2H, m), 1.34-1.70 (10H, m), 2.00 (1H, m), 2.57 (1H, br s), 3.44-3.55 (2H, m), 3.88 (1H, m), 4.00 (2H, s), 6.43 (1H, d, J = 7.8 Hz), 6.97 (1H, dd, J = 2.4 and 8.7 Hz), 7.25 (1H, d, J = 2.4 Hz), 7.65 (1H, s), 8.06 (1H, d, J = 8.7 Hz); IR ($CHCl_3$) 3599, 3437, 1780, 1649, 1603, 1516, 1124 cm^{-1}; $[\alpha]_D^{25}$ +36.4±0.8° (c=1.013, MeOH) Anal. ($C_{22}H_{27}NO_5S{\cdot}0.6H_2O$) Calcd. (%): C, 61.69; H, 6.64; N, 3.27; S, 7.49 Found (%): C, 61.58; H, 6.37; N, 3.54; S, 7.48
Ic-23	mp 149-151 °C; ^{1}H-NMR ($CDCl_3$) δ 1.08 (1H, m), 1.21-1.86 (12H, m), 1.99 (1H, m), 2.22 (2H, br s), 2.56 (1H, m), 3.53 (2H, t, J = 6.0 Hz), 3.92 (1H, m), 4.03 (2H, s), 6.31 (1H, d, J = 7.2 Hz), 7.00 (1H, dd, J = 2.1, 8.7 Hz), 7.67 (1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 2.4 Hz), 7.83 (1H, s); IR (Nujol) 3313, 3104, 2636, 1743, 1626, 1599, 1552, 1439, 1248, 1190, 1153, 1124 cm^{-1}; $[\alpha]_D^{26}$ +33.6±0.7° (c=1.002%, MeOH); Anal. ($C_{22}H_{27}NO_5S$) Calcd. (%):C, 63.29; H, 6.52; N, 3.35; S, 7.68Found (%):C, 62.99; H, 6.66; N, 3.39; S, 7.57
Ic-28	mp 149-151 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.21-1.72 (12H, m), 2.03 (1H, m), 2.56 (1H, br s), 3.48-3.60 (2H, m), 3.95 (1H, m), 4.04 (2H, s), 6.11 (1H, d, J = 8.1 Hz), 7.16 (1H, dt, J = 2.4, 8.7 Hz), 7.78 (1H, dd, J = 4.8, 8.7 Hz), 7.92 (1H, s), 8.05(1H, dd, J = 2.4, 9.9 Hz); IR (Nujol) 3384, 3361, 2546, 1736, 1718, 1616, 1533, 1225, 1140 cm^{-1}; $[\alpha]_D^{25}$ +35.6±0.8° (c=1.014, MeOH); Anal. ($C_{22}H_{26}FNO_4S$) Calcd. (%): C, 62.99; H, 6.25; F, 4.53; N, 3.34; S, 7.64 Found (%): C, 62.84; H, 6.51; F, 4.44; N, 3.41; S, 7.40
Ic-34	mp 154-157 °C; ^{1}H-NMR ($CDCl_3$) δ 1.09 (1H, m), 1.24-1.72 (12H, m), 2.04 (1H, m), 2.59 (1H, br s), 3.47-3.58 (2H, m), 4.02 (1H, m), 4.02 (2H, s), 6.42 (1H, d, J = 7.5 Hz), 7.38 (1H, d, J = 5.4 Hz), 7.43 (1H, d, J = 7.5 Hz), 7.59 (1H, d, J = 5.4 Hz), 7.61 (1H, d, J = 7.5 Hz), 7.96 (1H, dd, J = 0.9, 7.5 Hz); IR (Nujol) 3288, 2540, 1726, 1614, 1577, 1554, 1319, 1244, 1225, 1138 cm^{-1}; $[\alpha]_D^{25}$ +39.8±0.8° (c=1.017, MeOH); Anal. ($C_{22}H_{27}NO_4S$) Calcd. (%): C, 65.81; H, 6.78; N, 3.49; S. 7.99 Found (%): C, 65.53: H, 6.94; N. 3.52; S. 7.76

Table 39

Compound No.	Physical property
Ic-39	^{1}H-NMR ($CDCl_3$) δ 1.10 (1H, m), 1.25-1.71 (12H, m), 2.03 (1H, m), 2.58 (1H, br s), 3.49-3.56 (2H, m), 3.98 (3H, s), 4.02 (2H, s), 4.03 (1H, m), 6.40 (1H, d, J = 8.4 Hz), 6.42 (2H, s), 7.42 (1H, t, J = 7.5 Hz), 7.66 (1H, d, J = 7.5 Hz), 7.93 (1H, d, J = 7.5 Hz) ; IR ($CHCl_3$) 3451, 1780, 1732, 1649, 1508, 1373, 1220, 1151 cm^{-1}; $[\alpha]_D^{24}$ +37.0±0.8° (c=1.008, MeOH); Anal. ($C_{23}H_{29}NO_5S \cdot 0.3H_2O$) Calcd. (%): C, 63.22; H, 6.83; N, 3.21; S, 7.34 Found (%): C, 63.26; H, 6.78; N, 3.23; S, 7.17
Ic-49	^{1}H-NMR ($CDCl_3$) δ 1.06 (1H, m), 1.29-1.36 (2H, m), 1.36-1.74 (10H, m), 2.03 (1H, m), 2.53 (1H, m), 3.45 (3H, s), 3.52 (2H, dt, J = 6.3, 1.5 Hz), 4.00 (1H, m), 4.02 (2H, s), 4.79 (2H, s), 6.07 (1H, d, J = 7.8 Hz), 7.33-7.40 (2H, m), 7.77 (1H, dd, J = 6.9, 2.1 Hz), 8.16 (1H, s) ; IR ($CHCl_3$) 3440, 2829, 1652, 1573, 1509, 1226, 1205, 1124 cm^{-1}; $[\alpha]_D^{25.0}$ +33.3±0.7° (c=1.016, MeOH); Anal. ($C_{24}H_{31}NO_6$) Calcd. (%): C, 67.11; H, 7.27; N, 3.26Found (%): C, 66.82; H, 7.39; N, 3.32
Ic-51	^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.08 (1H, m), 1.25-1.28 (2H, m), 1.37-1.62 (10H, m), 1.99 (1H, d, J = 3.3 Hz), 2.54 (1H, s), 3.45-3.49 (2H, m), 3.87 (1H, m), 4.00 (2H, s), 6.44 (1H, d, J = 7.8 Hz), 6.88 (1H, dd, J = 2.1, 8.7 Hz), 6.97 (1H, d, J = 2.1 Hz), 7.60 (1H, d, J = 8.7 Hz), 8.02 (1H, s); IR (KBr) 3365, 3140, 1734, 1628, 1560, 1527, 1493, 1440, 1363, 1279, 1220, 1136, 1124 cm^{-1}; $[\alpha]_D^{27}$ +29.1±0.7° (c=1.016, MeOH); Anal. ($C_{22}H_{27}NO_6 \cdot 0.5H_2O$) Calcd. (%): C, 64.38; H, 6.88; N, 3.41Found (%): C, 64.39; H, 6.95; N, 3.66
Ic-52	^{1}H-NMR ($CDCl_3 \cdot CD_3OD$) δ 1.07 (1H, m), 1.24-1.30 (3H, m), 1.45-1.49 (5H, m), 1.59-1.65 (4H, m), 2.00 (1H, d, J = 3.3 Hz), 2.59 (1H, s), 3.52 (2H, t, J = 6.0 Hz), 3.89 (1H, m), 4.00 (1H, d, J = 16.5 Hz), 4.06 (1H, d, J = 16.5 Hz), 6.14 (1H, d, J = 8.1 Hz), 6.90 (1H, dd, J = 2.1, 9.0 Hz), 7.34 (1H, d, J = 2.1 Hz), 7.36 (1H, d, J = 9.0 Hz), 8.06 (1H, s); IR ($CHCl_3$) 3438, 3267, 1730, 1647, 1620, 1558, 1514, 1468, 1169, 1134 cm^{-1}; $[\alpha]_D^{27}$ +25.0±0.7° (c=1.003, MeOH); Anal. ($C_{22}H_{27}NO_6 \cdot 0.3H_2O$) Calcd. (%): C, 64.95; H, 6.84; N, 3.44Found (%): C, 64.84; H. 6.96; N, 3.62
Ic-54	^{1}H-NMR ($CDCl_3$) δ 1.04 (1H, m), 1.25-1.32 (2H, m), 1.43-1.68 (10H, m), 2.03 (1H, m), 2.53 (1H, m), 3.53 (2H, t, J = 6.6 Hz), 3.96 (1H, m), 4.04 (2H, s), 6.04 (1H, d, J = 8.1 Hz), 7.09-7.16 (1H, m), 7.25 (1H, dd, J = 8.4, 2.4 Hz), 7.84 (1H, dd, J = 8.4, 5.7 Hz), 8.10 (1H, s) ; IR ($CHCl_3$) 3440, 2875, 1656, 1563, 1506, 1224, 1216, 1205 cm^{-1}; $[\alpha]_D^{26.0}$ +27.6±0.7° (c=1.018, MeOH); Anal. ($C_{22}H_{26}FNO_5 \cdot 0.6H_2O$) Calcd. (%): C, 63.79; H, 6.62; F, 4.59; N, 3.38 Found (%): C, 63.48; H, 6.49; F, 4.47; N, 3.59
Ic-65	mp 148-149°C, ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.27-1.30 (2H, m), 1.41-1.52 (6H, m), 1.59-1.71 (4H, m), 2.01 (1H, d, J = 3.3 Hz), 2.45 (1H, s), 3.53 (2H, dt, J = 1.5, 6.3 Hz), 3.94 (1H, m), 4.07 (2H, s), 6.13 (1H, d, J = 8.1 Hz), 6.78 (1H, d, J = 1.5 Hz), 6.98 (1H, d, J = 5.1 Hz), 7.23 (1H, d, J = 5.1 Hz), 10.27 (1H, s); IR (KBr) 3367, 3292, 3111, 2758, 2636, 2544, 1712, 1601, 1574, 1510, 1458, 1325, 1250, 1225, 1138 cm^{-1}; $[\alpha]_D^{25}$ +66.6±1.1° (c=1.008, MeOH); Anal. ($C_{20}H_{26}N_2O_4S \cdot 0.1H_2O$) Calcd. (%): C, 61.23; H, 6.68; N, 7.14; S, 8.17Found (%): C, 61.20; H, 6.79; N, 7.25; S, 8.25

Table 40

Compound No.	Physical property
Ic-66	mp 143-144 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.24-1.30 (2H, m), 1.38-1.52 (6H, m), 1.59-1.67 (4H, m), 2.01 (1H, d, J = 3.0 Hz), 2.48 (1H, s), 3.52 (2H, t, J = 6.3 Hz), 3.94 (1H, m), 4.07 (2H, s), 6.12 (1H, d, J = 8.4 Hz), 6.73 (1H, d, J = 1.8 Hz), 6.88 (1H, d, J = 5.4 Hz), 6.93 (1H, d, J = 5.4 Hz), 10.80 (1H, s); IR (KBr) 3348, 3105, 2754, 2648, 2551, 1738, 1587, 1556, 1520, 1437, 1425, 1223, 1146 cm^{-1}; $[\alpha]_D^{25}$ +50.5±0.9° (c=1.014, MeOH); Anal. ($C_{20}H_{26}N_2O_4S \cdot 0.1H_2O$) Calcd. (%): C, 61.23; H, 6.68; N, 7.14; S, 8.17 Found (%): C, 61.13; H, 6.79; N, 7.17; S, 8.07

Table 40 (continued)

Compound No.	Physical property
Ic-81	^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.06 (1H, m), 1.20-1.28 (2H, m), 1.34-1.49 (6H, m), 1.55-1.63 (4H, m), 1.95 (1H, d, J = 3.6 Hz), 2.42 (3H, s), 2.56 (1H, brs), 3.48 (2H, t, J = 6.5 Hz), 3.84 (1H, br s), 4.01 (2H, s), 6.37 (1H, d, J = 7.5 Hz), 6.71 (1H, d, J = 2.1 Hz), 7.16 (1H, d, J = 2.1 Hz), 8.10 (1H, s); IR (KBr) 3361, 3134, 1734, 1635, 1560, 1529, 1458, 1415, 1362, 1288, 1198, 1165, 1136 cm^{-1}; $[\alpha]_D^{24}$ +28.1±0.7° (c=1.012, MeOH) Anal. ($C_{23}H_{29}NO_6 \cdot 0.5H_2O$) Calcd. (%): C, 65.08; H, 7.12; N, 3.30 Found (%): C, 65.14; H, 7.06; N, 3.43
Ic-84	mp 133-135 °C ; ^{1}H-NMR ($CDCl_3$) δ 1.09 (1H, m), 1.22-1.70 (12H, m), 2.01 (1H, d, J = 3.3 Hz), 2.55 (1H, br s), 3.50-3.68 (2H, m), 3.96-4.09 (3H, m), 4.21-4.35 (2H, m), 6.11 (1H, m), 7.64 (1H, dd, J = 1.8, 8.7 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.85 (1H, br s), 8.18 (1H, br s); IR (Nujol) 3323, 2924, 1736, 1599, 1562, 1514, 1448, 1281, 1217, 1142 cm^{-1}; $[\alpha]_D^{24}$ +21.7±0.6° (c=1.017%, MeOH); Anal. ($C_{25}H_{32}N_2O_6S$) Calcd. (%): C, 61.45; H, 6.60; N, 5.73; S, 6.56 Found (%): C, 61.26; H, 6.41; N, 5.70; S, 6.48
Ic-86	^{1}H-NMR ($CDCl_3$) δ 1.16-1.69 (13H, m), 1.92 (1H, br s), 2.39 (1H, br s), 3.41 (2H, t, J = 5.4 Hz), 3.68 (1H, m), 3.92 (2H, s), 5.83 (2H, s), 7.65 (1H, dd, J = 2.1, 8.7 Hz), 7.83 (1H, d, J = 8.7 Hz), 8.23 (1H, d, J = 8.4 Hz), 8.25 (1H, s), 8.27 (1H, d, J = 2.1 Hz), 8.77 (1H, s), 12.53 (1H, br s); IR (Nujol) 3332, 2924, 1724, 1680, 1631, 1572, 1529, 1444, 1375, 1350, 1244, 1128 cm^{-1}; $[\alpha]_D^{24}$ +23.6±0.6° (c=1.014%, MeOH); Anal. ($C_{23}H_{29}N_3O_5S \cdot 0.4H_2O$) Calcd. (%): C, 59.18; H, 6.43; N, 9.00; S, 6.87 Found (%): C, 59.33; H, 6.48; N, 8.87; S, 6.48
Ic-95	mp 118-120 °C; ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ 1.16 (1H, m), 1.26 (3H, t, J = 7.2 Hz), 1.27-1.66 (12H, m), 2.01 (1H, m), 2.59 (1H, m), 3.52 (2H, m), 3.90 (1H, m), 4.00 (2H, s), 4.14 (2H, q, J = 7.2 Hz), 4.48 (2H, br s), 5.62 (1H, br s), 6.68 (1H, br s), 7.38 (1H, br d, J = 8.7 Hz), 7.81 (1H, d, J = 8.7 Hz), 7.96 (1H, s), 8.31 (1H, br s); IR ($CHCl_3$) 3442, 1724, 1655, 1516, 1477, 1435, 1225, 1217, 1132, 1059 cm^{-1}; $[\alpha]_D^{23}$ +25.9±0.7° (c=1.012, MeOH) Anal. ($C_{26}H_{34}N_2O_6S \cdot 0.2H_2O$) Calcd. (%): C, 61.69; H, 6.85; N, 5.53; S, 6.33 Found (%): C, 61.71; H, 6.73; N, 5.48; S, 6.32

Table 41

Compound No.	Physical property
Ic-99	^{1}H-NMR (d_6-DMSO) δ 1.19-1.68 (13H, m), 1.93 (1H, br s), 2.43 (1H, br s), 3.41 (2H, t, J = 6.6 Hz), 3.49 (2H, s), 3.71 (1H, m), 3.92 (2H, s), 7.38 (1H, br s), 7.87 (1H, dd, J = 1.8, 8.7 Hz), 8.07 (1H, br s), 8.09 (1H, d, J = 8.4 Hz), 8.35 (1H, d, J = 6.6 Hz), 8.39 (1H, s), 8.85 (1H, d, J = 1.2 Hz); IR (Nujol) 3340, 3251, 2927, 1741, 1655, 1624, 1539, 1458, 1377, 1244, 1134 cm^{-1}; $[\alpha]_D^{25}$ +24.2±0.6° (c=1.009%, MeOH); Anal. ($C_{23}H_{28}N_2O_5S \cdot 0.5H_2O$) Calcd. (%): C, 60.91; H, 6.44; N, 6.18; S, 7.07 Found (%): C, 60.89; H, 6.57; N, 5.80; S, 6.91
Ic-115	mp 133-135 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.21-1.34 (2H, m), 1.40-1.72 (10H, m), 2.02 (1H, m), 2.47 (3H, s), 2.53 (3H, s), 2.57 (1H, br s), 3.48-3.59 (2H, m), 3.97 (1H, m), 4.03 (2H, s), 6.12 (1H, d, J = 7.5 Hz), 7.05 (1H, s), 7.84 (1H, s), 7.94 (1H, s) ; IR (Nujol) 3344, 2540, 1730, 1614, 1539, 1219, 1142 cm^{-1}; $[\alpha]_D^{25}$ +34.7±0.7° (c=1.012, MeOH) Anal. ($C_{23}H_{29}NO_4S$) Calcd. (%): C, 67.10; H, 7.27; N, 3.26; S, 7.64 Found (%): C, 66.81; H, 7.50; N, 3.18; S, 7.32
Ic-128	^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.19-1.68 (12H, m), 1.99 (1H, br s), 2.57 (1H, br s), 3.48 (2H, t, J = 6.3 Hz), 3.49 (2H, s), 3.95 (1H, m), 3.99 (2H, s), 4.85 (2H, br s), 6.27 (1H, d, J = 8.1 Hz), 7.47 (1H, d, J = 9.9 Hz), 7.76 (1H, s), 8.07 (1H, d, J = 8.4 Hz); IR ($CHCl_3$) 3435, 3192, 2954, 1730, 1637, 1520, 1435, 1275 cm^{-1}; $[\alpha]_D^{26}$ +29.9±0.7° (c=1.011%, MeOH); Anal. ($C_{22}H_{26}NO_5SF \cdot 0.4H_2O$) Calcd. (%): C, 59.20; H, 6.14; N, 3.14; S, 7.18; F, 4.26 Found (%): C, 59.16; H, 5.90; N, 3.05; S, 7.09; F, 4.14

Table 41 (continued)

Compound No.	Physical property
Ic-129	mp 135-137 °C; ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, m), 1.22-1.69 (12H, m), 2.04 (1H, br s), 2.56 (1H, br s), 3.54 (2H, dt, J = 1.5, 6.6 Hz), 3.96 (1H, m), 3.98 (3H, s), 4.03 (2H, s), 6.12 (1H, d, J = 6.9 Hz), 7.52 (1H, d, J = 10.5 Hz), 7.77 (1H, s), 8.04 (1H, d, J = 8.4 Hz); IR (Nujol) 3334, 2924, 1745, 1618, 1535, 1498, 1462, 1415, 1281, 1259 cm^{-1}; $[\alpha]_D^{24}$ +23.6±0.6° (c=1.014%, MeOH); Anal. ($C_{23}H_{28}NO_5SF$) Calcd. (%): C, 61.45; H, 6.28; N, 3.12; S, 7.13; F, 4.23 Found (%): C, 61.17; H, 6.33; N, 3.03; S, 7.04; F, 4.03
Ic-135	^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ 1.17 (1H, m), 1.26-1.66 (12H, m), 2.00 (1H, m), 2.56 (1H, m), 3.53 (2H, t, J = 6.3 Hz), 3.86 (1H, m), 4.01 (2H, s), 6.62 (1H, br d, J = 8.1 Hz), 7.40 (2H, br s), 7.96 (1H, s), 8.17 (1H, s); IR (nujol) 1726, 1633, 1556, 1303, 1252, 1176, 1130 cm^{-1}; $[\alpha]_D^{24}$ +19.5±0.6° (c=1.009, MeOH)
Ic-140	mp 96-98 °C; ^{1}H-NMR (DMSO-d_6) δ 1.18-1.31 (8H, m), 1.49-1.56 (5H, m), 1.94 (1H, m), 2.38 (1H, br s), 3.40 (2H, t, J = 6.5 Hz), 3.47 (2H, s), 3.68(111, m), 3.93 (2H, s), 6.88 (1H, br s), 7.26 (1H, dd, J= 1.5 and 8.7 Hz), 7.50 (1H, br s), 7.54 (1H, d, J = 8.7 Hz), 7.94 (1H, d, J = 1.5 Hz), 8.12 (1H, d, J = 6.6 Hz), 8.59 (1H, s), IR (Nujol) 3386, 3276, 3195, 3064, 2549, 1747, 1697, 1666, 1624, 1560, 1128 cm^{-1}; $[\alpha]_D^{25}$ +22.0±0.6° (c=1.006, MeOH) Anal. ($C_{24}H_{30}N_2O_6 \cdot 0.8H_2O$) Calcd. (%): C, 63.09; H, 6.97; N, 6.13 Found (%): C, 63.18; H, 6.98; N, 5.94

Table 42

Compound No.	Physical property
Ic-142	^{1}H-NMR ($CDCl_3$-CD_3OD) δ 1.19 (1H, m), 1.26-1.31 (2H, m), 1.39-1.64 (10H, m), 1.98 (1H, m), 2.55 (1H, br s), 3.50 (2H, t, J = 6.3 Hz), 3.86 (1H, m), 4.01 (2H, s), 6.44 (1H, br s), 6.88 (1H, d, J = 7.2 Hz), 7.29 (1H, br s), 7.50 (1H, d, J = 8.4 Hz), 7.89 (1H, dd, J = 1.8 and 8.4 Hz), 8.22 (1H, s), 8.45 (1H, d, J = 1.8 Hz); IR ($CHCl_3$) 3026, 3014,2875, 1728, 1662, 1587, 1562, 1510,1126 cm^{-1}; $[\alpha]_D^{25}$ +19.6±0.6° (c=1.008, MeOH) Anal. ($C_{23}H_{28}N_2O_6 \cdot 0.5H_2O$) Calcd. (%): C, 63.14; H, 6.68; N, 6.40 Found (%): C, 63.02; H, 6.49; N, 6.35
Ie-34	^{1}H-NMR ($CDCl_3$) δ 1.08 (1H, m), 1.23-1.71 (12H, m), 2.03 (1H, d, J = 3.3 Hz), 2.60 (1H, br s), 2.63 (2H, t, J = 6.9 Hz), 3.18 (2H, br s), 4.03 (1H, m), 6.45 (1H, d, J = 7.5 Hz), 7.38 (1H, d, J = 5.7 Hz), 7.42 (1H, t, J = 7.5 Hz), 7.58 (1H, d, J = 5.4 Hz), 7.63 (1H, d, J = 6.9 Hz), 7.96 (1H, d, J = 7.8 Hz); IR ($CHCl_3$) 3452, 2954, 1711, 1649, 1520, 1495, 1458, 1300, 1284 cm^{-1}; $[\alpha]_D^{26}$ +38.1±1.6° (c=0.502%, MeOH); Anal. ($C_{22}H_{27}NO_3S_2 \cdot 0.3H_2O$) Calcd. (%):C, 62.47; H, 6.58; N, 3.31; S, 15.16 Found (%):C, 62.53; H, 6.63; N, 3.38; S, 15.16
Ie-49	^{1}H-NMR ($CDCl_3$) δ 1.07 (1H, m), 1.29-1.68 (12H, m), 2.01 (1H, m), 2.55 (1H, m), 2.64 (2H, t, J = 7.5 Hz), 3.18 (2H, s), 3.44 (3H, s), 3.99 (1H, m), 4.78 (2H, s), 6.12 (1H, d, J = 7.2 Hz), 7.33-7.40 (2H, m), 7.79 (1H, dd, J = 6.9, 1.8 Hz), 8.17 (1H, s); IR ($CHCl_3$) 3440, 2670, 1710, 1650, 1573, 1562, 1509, 1425, 1297, 1238, 1224 cm^{-1}; $[\alpha]_D^{24.0}$ +33.2±0.7° (c=1.019, MeOH); Anal. ($C_{24}H_{31}NO_5S \cdot 0.2H_2O$) Calcd. (%): C, 64.18; H, 7.05; N, 3.12Found (%): C, 64.11; H, 7.11; N, 3.24
IIa-22	^{1}H-NMR ($CDCl_3$) δ 0.94 (1H, d, J = 10.2 Hz), 1.11 (3H, s), 1.23 (3H, s), 1.34-1.54 (6H, m), 1.65-1.89 (2H, m), 2.00 (1H, m), 2.13-2.39 (5H, m), 4.32 (1H, m), 5.75 (1H, dt, J = 15.9, 1.2 Hz), 6.22 (1H, d, J = 8.7 Hz), 6.98 (1H, dd, J = 2.1, 9.0 Hz), 6.99 (1H, td, J = 7.2, 15.9 Hz), 7.26 (1H, d, J = 2.1 Hz), 7.58 (1H, s), 8.08 (1H, d, J = 9.0 Hz); IR (KBr) 3300, 1695, 1603, 1522, 1468, 1417, 1236 cm^{-1}; $[\alpha]_D^{26}$ +31.3±0.7° (c=1.000, MeOH); Anal. ($C_{25}H_{31}NO_4S \cdot 0.4H_2O$) Calcd. (%): C, 66.91; H, 7.14; N, 3.12; S, 7.14 Found (%): C, 66.81; H, 7.05; N, 3.13; S, 7.07
IIa-23	mp 189-192 °C; ^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.28-2.39 (14H, m), 4.31 (1H, m), 5.78 (1H, d, J = 15.6 Hz), 6.19 (1H, d, J = 9.6 Hz), 6.99 (1H, m), 7.01 (1H, dd, J = 8.7, 2.7 Hz), 7.66 (1H, d, J = 8.7 Hz), 7.67 (1H, s), 7.89 (1H, d, J = 2.7 Hz); IR (Nujol) 3199, 2683, 1684, 1635, 1599, 1525, 1437, 1304, 1286, 1225 cm^{-1}; $[\alpha]_D^{26\,0}$ +26.8±0.7° (c=1.011, MeOH); Anal. ($C_{25}H_{31}NO_4S \cdot 0.3H_2O$) Calcd. (%): C, 68.00; H, 7.08; N, 3.17; S, 7.26 Found (%): C, 68.09; H, 6.94; N, 3.16; S, 7.18

Table 43

Compound No.	Physical property
IIa-24	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 9.9 Hz), 1.15 (3H, s), 1.27 (3H, s), 1.32-1.60 (6H, m), 1.66-1.90 (2H, m), 2.04 (1H, m), 2.17-2.43 (5H, m), 4.29 (1H, m), 5.79 (1H, d, J = 15.6 Hz), 6.49 (1H, d, J = 9.0 Hz), 6.93 (1H, dd, J = 2.7, 5.7 Hz), 7.02 (1H, td, J = 6.9, 15.6 Hz), 7.31 (1H, d, J = 2.7 Hz), 7.32 (1H, t, J = 5.7 Hz), 7.65 (1H, s), 12.09 (1H, s); IR ($CHCl_3$) 3521, 3454, 2686, 1695, 1651, 1624, 1585, 1562, 1522, 1456, 1271 cm^{-1}; $[\alpha]_D^{27}$ +29.4±0.7° (c=1.004, MeOH); Anal. ($C_{25}H_{31}NO_4S\cdot 0.4H_2O$) Calcd. (%): C, 66.91; H, 7.14; N, 3.12; S, 7.14 Found (%): C, 66.97; H, 7.01; N, 3.23; S, 7.17
IIa-28	mp 172-174°C; ^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 9.9 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.30-2.42 (14H, m), 4.31 (1H, m), 5.79 (1H, dt, J =15.6, 1.5 Hz), 6.08 (1H, d, J = 9.3 Hz), 7.03 (1H, dt, J = 15.6, 7.2 Hz), 7.17 (1H, dt, J = 8.7, 2.7 Hz), 7.80 (1H, dd, J = 8.7, 5.1 Hz), 7.83 (1H, s), 8.07 (1H, dd, J = 10.2, 2.7 Hz); IR (Nujol) 3374, 2719, 1698, 1650, 1627, 1525, 1442, 1431 cm^{-1}; $[\alpha]_D^{24.0}$ +28.2±0.7° (c=1.012, MeOH); Anal. ($C_{30}H_{37}NO_4S\cdot 1.1H_2O$) Calcd. (%):Calcd. (%): C, 67.57; H, 6.50; N, 3.15; S, 7.22 Found (%): C, 67.35; H, 6.76; N, 3.26; S, 7.12
IIa-34	mp 141-142°C; ^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 9.9 Hz), 1.16 (3H, s), 1.24 (3H, s), 1.29-2.42 (14H, m), 4.39 (1H, m), 5.77 (1H, d, J = 15.6 Hz), 6.43 (1H, d, J = 8.7 Hz), 7.01 (1H, dt, J = 15.6, 3.6 Hz), 7.38 (1H, d, J = 5.4 Hz), 7.43 (1H, t, J = 7.5 Hz), 7.54 (1H, d, J = 7.5 Hz), 7.59 (1H, d, J = 5.4 Hz), 7.96 (1H, d, J = 7.5 Hz); IR (Nujol) 3380, 2686, 1699, 1619, 1581, 1461, 1234, 1200 cm^{-1}; $[\alpha]_D^{25\,0}$ +48.8±0.9° (c=1.009, MeOH); Anal. ($C_{25}H_{31}NO_3S$) Calcd. (%): C, 70.55; H, 7.34; N, 3.29; S, 7.53 Found (%): C, 70.35; H, 7.33; N, 3.31; S, 7.44
IIa-51	mp 211-213 °C; ^{1}H-NMR ($CDCl_3$-CD_3OD) δ 0.94 (1H, d, J = 9.9 Hz), 1.15 (3H, s), 1.24 (3H, s), 1.36-1.55 (6H, m), 1.70 (1H, m), 1.83 (1H, m), 2.02 (1H, m), 2.15-2.38 (5H, m), 4.29 (1H, m), 5.74 (1H, d, J = 15.6 Hz), 6.90 (1H, dd, J = 2.1, 8.7 Hz), 6.90 (1H, dt, J = 15.6, 6.9 Hz), 7.00 (1H, d, J = 2.1 Hz), 7.56 (1H, d, J = 8.7 Hz), 7.99 (1H, s); IR (KBr) 3425, 3255, 2600, 1938, 1685, 1626, 1605, 1579, 1522 1442, 1265, 1146, 1128, 1107 cm^{-1}; $[\alpha]_D^{27}$ +23.9±0.6° (c=1.004, MeOH); Anal. ($C_{25}H_{31}NO_5\cdot 0.1H_2O$) Calcd. (%): C, 70.27; H, 7.36; N, 3.28 Found (%): C, 70.13; H, 7.34; N, 3.47
IIa-52	mp 159-160 °C; ^{1}H-NMR ($CDCl_3$) δ 0.92 (1H, d, J = 9.9 Hz), 1.11 (3H, s), 1.21 (3H, s), 1.36-1.50 (6H, m), 1.63 (1H, m), 1.79 (1H, m), 1.98 (1H, s), 2.10-2.20 (4H, m), 2.30 (1H, s), 4.30 (1H, s), 5.69 (1H, d, J = 15.6 Hz), 6.20 (1H, d, J = 9.0 Hz), 6.91 (1H, dd, J = 2.4, 9.0 Hz), 6.94 (1H, dt, J = 15.6, 6.9 Hz), 7.33 (1H, d, J = 9.0 Hz), 7.56 (1H, d, J = 2.4 Hz), 7.98 (1H, s); IR (KBr) 3255, 2688, 1684, 1643, 1560, 1522, 1306, 1288, 1269, 1219, 1192, 1167, 1134 cm^{-1}; $[\alpha]_D^{25}$ +21.8±0.6° (c=1.020, MeOH); Anal. ($C_{25}H_{31}NO_5$) Calcd. (%): C, 70.57; H, 7.34; N, 3.29 Found (%): C, 70.41; H, 7.16; N, 3.34

Table 44

Compound No.	Physical property
IIa-54	^{1}H-NMR ($CDCl_3$) δ 0.95 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.24 (3H, s), 1.32-1.57 (6H, m), 1.69-1.88 (2H, m), 2.02 (1H, m), 2.16-2.24 (4H, m), 2.35 (1H, m), 4.32 (1H, m), 5.78 (1H, dt, J = 15.3, 1.5 Hz), 6.02 (1H, d, J = 9.0 Hz), 7.02 (1H, dt, J = 15.3, 6.9 Hz),7.09-7.15 (1H, m), 7.26 (1H, dd, J = 8.7, 2.1 Hz), 7.82 (1H, dd, J = 8.7, 5.4 Hz), 8.05 (1H, s) ; IR ($CHCl_3$) 3446, 2680, 1695, 1652, 1257, 1220, 1214 cm^{-1}; $[\alpha]_D^{25.0}$ +23.3±0.6° (c=1.008, MeOH); Anal. ($C_{25}H_{30}FNO_4\cdot 0.4H_2O$) Calcd. (%): C, 69.07; H, 7.14; F, 4.37; N, 3.22 Found (%): C, 68.82; H, 6.89; F, 4.49; N, 3.34

Table 44 (continued)

Compound No.	Physical property
II a -66	^{1}H-NMR ($CDCl_3$) δ 0.95 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.24 (3H, s), 1.40-1.55 (6H, m), 1.70-1.85 (2H, m), 2.00 (1H, br s), 2.12- 2.37 (5H, m), 4.30 (1H, m), 5.80 (1H, d, J = 15.6 Hz), 6.17 (1H, d, J = 9.0 Hz), 6.68 (1H, d, J = 2.1 Hz), 6.88 (1H, d, J = 5.4 Hz), 6.94 (1H, d, J = 5.4 Hz), 7.03 (1H, dt, J = 15.6 and 6.9 Hz), 11.22 (1H, s); IR ($CHCl_3$) 3448, 3188, 1693, 1637, 1543, 1518, 1471, 1421, 1396, 1385, 1257, 1232 cm^{-1}; $[\alpha]_D^{26}$ +18.2±0.6° (c=1.005, MeOH) Anal. ($C_{23}H_{30}N_2O_3S\cdot 0.2H_2O$) Calcd. (%): C, 66.06; H, 7.33; N, 6.70; S, 7.66 Found (%): C, 66.19; H, 7.06; N, 6.83; S, 7.35
IIa-81	mp 167-168 °C; ^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.23 (3H, s), 1.33-1.54 (6H, m), 1.64 (1H, m), 1.80 (1H, m), 1.99 (1H, br s), 2.12- 2.38 (5H, m), 2.44 (3H, s), 4.31 (1H, m), 5.71 (1H, d, J = 15.6 Hz), 6.08 (1H, d, J = 9.6 Hz), 6.72 (1H, d, J = 2.1 Hz), 6.97 (1H, dt, J = 15.6 and 6.9 Hz), 7.30 (1H, d, J = 2.1 Hz), 7.97 (1H, s); IR (KBr) 3276, 2686, 1693, 1643, 1610, 1562, 1518, 1460, 1417, 1385, 1367, 1284, 1200, 1136 cm^{-1}; $[\alpha]_D^{24}$ +23.0±0.6° (c=1.020, MeOH) Anal. ($C_{26}H_{33}NO_5\cdot 0.2H_2O$) Calcd. (%): C, 70.47; H, 7.60; N, 3.16 Found (%): C, 70.50; H, 7.47; N, 3.35
IIa-94	^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.25 (3H, s), 1.42-1.56 (6H, m), 1.70-1.88 (2H, m), 2.00 (1H, m), 2.03 (3H, s), 2.18-2.38 (5H, m), 4.31 (1H, m), 4.55 (2H, m), 5.78 (1H, d, J = 15.6 Hz), 6.18-6.23 (2H, m), 6.98 (1H, dt, J = 15.6, 6.9 Hz), 7.34 (1H, dd, J = 1.8, 8.4 Hz), 7.77 (1H, s), 7.79 (1H, d, J = 8.4 Hz), 8.31 (1H, br s); IR ($CHCl_3$) 3446, 1695, 1655, 1514, 1471, 1435, 1369, 1222, 1215 cm^{-1}; $[\alpha]_D^{24}$ +23.4±0.6° (c=1.006, MeOH) Anal. ($C_{28}H_{36}N_2O_4S\cdot 0.4H_2O$) Calcd. (%): C, 66.74; H, 7.36; N, 5.56; S, 6.36 Found (%): C, 66.79; H, 7.23; N, 5.51; S, 6.39
IIa-99	mp 130-133 °C ; 0.85 (1H, d, J = 9.6 Hz), 1.12 and 1.19 (3H, s), 1.25-2.38 (12H, m), 3.99 (1H, m), 5.72 (1H, d, J = 15.6 Hz), 6.79 (1H, dt, J = 6.6, 15.6 Hz), 7.38 (1H, s), 7.87 (1H, dd, J = 1.8, 8.7 Hz), 8.05-8.13 (3H, m), 8.31 (1H, s), 8.82 (1H, d, J = 1.2 Hz); IR (Nujol) 3375, 3178, 2918, 1703, 1653, 1626, 1527, 1460, 1398, 1255 cm^{-1}; $[\alpha]_D^{25}$ +27.9±0.7° (c=1.011%, MeOH); Anal. ($C_{26}H_{32}N_2O_4S\cdot 0.7$AcOEt) Calcd. (%): C, 65.23; H, 7.15; N, 5.28; S, 6.05 Found (%): C, 64.99; H, 6.91; N, 5.52; S, 6.18

Table 45

Compound No.	Physical property
IIb-28	^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.26 (3H, s), 1.59 (1H, ddd, J = 2.7, 5.7, 13.5 Hz), 1.95-2.57 (7H, m), 4.06-4.27 (4H, m), 4.33 (1H, m), 5.60-5.80 (2H, m), 6.18 (1H, d, J = 9.0 Hz), 7.17 (1H, dt, J = 3.0, 9.0 Hz), 7.79 (1H, dd, J = 4.8, 8.7 Hz), 7.89 (1H, s), 8.04 (1H, dd, J = 2.7, 9.9 Hz); IR ($CHCl_3$) 3442, 3022, 1734, 1651, 1603, 1564, 1516, 1496, 1471, 1433, 1244, 1119 cm^{-1}; $[\alpha]_D^{25}$ +43.8±1.4° (c=1.003%, MeOH); Anal. ($C_{24}H_{28}NO_4SF\cdot 0.4H_2O$) Calcd. (%):C, 63.67; H, 6.41; F, 4.20; N, 3.09; S, 7.08 Found (%):C, 63.73; H, 6.35; F, 4.11; N, 3.20; S, 7.07
IIc-04	mp 132-134 °C; ^{1}H-NMR ($CDCl_3$) δ 0.94 (1H, d, J = 9.9 Hz), 1.13 (3H, s), 1.23 (3H, s), 1.40-1.86 (8H, m), 2.00 (1H, m), 2.13 (1H, m), 2.18-2.37 (2H, m), 3.53 (2H, t, J = 6.0 Hz), 4.04 (2H, s), 4.28 (1H, m), 6.14 (1H, d, J = 9.0 Hz), 7.31-7.36 (2H, m), 7.85 (1H, m); IR (Nujol) 3373, 3105, 2528, 1736, 1601, 1556, 1215, 1138 cm^{-1}; $[\alpha]_D^{25}$ +22.7±0.6° (c=1.004, MeOH); Anal. ($C_{20}H_{29}NO_4S$) Calcd. (%): C, 63.30; H, 7.70; N, 3.69; S, 8.45 Found (%): C, 63.10; H, 7.73; N, 3.74; S, 8.34
IIc-17	mp 125-126 °C; ^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.40-1.93 (8H, m), 2.02 (1H, m), 2.17-2.41 (3H, m), 3.53 (2H, t, J = 6.3 Hz), 4.02 (2H, s), 4.36 (1H, m), 6.21 (1H, d, J = 9.0 Hz), 7.37-7.49 (2H, m), 7.84 (1H, s), 7.87 (1H, m), 8.30 (1H, m); IR (Nujol) 3282, 2540, 1724, 1604, 1554, 1246, 1228, 1130, 1109 cm^{-1}; $[\alpha]_D^{25}$ +29.6±0.7° (c=1.013, MeOH); Anal. ($C_{24}H_{31}NO_4S$) Calcd. (%): C, 67.10; H, 7.27; N, 3.26; S, 7.46 Found (%): C, 66.88; H, 7.10; N, 3.30; S, 7.25

Table 45 (continued)

Compound No.	Physical property
IIc-19	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.24 (3H, s), 1.40-1.92 (8H, m), 2.01 (1H, m), 2.17-2.40 (3H, m), 2.48 (3H, s), 3.47-3.58 (2H, m), 3.97 (1H, m), 4.02 (2H, s), 4.34 (1H, m), 6.21 (1H, d, J = 9.3 Hz), 7.28 (1H, m), 7.65 (1H, m), 7.75 (1H, s), 8.16 (1H, d, J = 8.4 Hz); IR ($CHCl_3$) 3442, 2567, 1780, 1732, 1649, 1514, 1242, 1134 cm^{-1}; $[\alpha]_D^{25}$ +28.7±0.8° (c=1.003, MeOH) Anal. ($C_{25}H_{33}NO_4S\cdot0.4H_2O$) Calcd. (%): C, 66.61; H, 7.56; N, 3.11; S, 7.11 Found (%): C, 66.67; H, 7.37; N, 3.03; S, 6.88
IIc-20	mp 87-90 °C; ^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.5 Hz), 1.14 (3H, s), 1.26 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.18-2.41 (3H, m), 2.49 (3H, s), 3.54 (2H, t, J = 6.0 Hz), 4.02 (2H, s), 4.35 (1H, m), 6.20 (1H, d, J = 8.4 Hz), 7.23 (1H, dd, J = 0.6, 8.4 Hz), 7.74 (1H, d, J = 8.4 Hz), 7.80 (1H, s), 8.11 (1H, d, J = 0.6 Hz); IR (Nujol) 3411, 3357, 1736, 1604, 1531, 1219, 1134 cm^{-1}; $[\alpha]_D^{25}$ +27.4±0.7° (c=1.013, MeOH); Anal. ($C_{25}H_{33}NO_4S\cdot0.3H_2O$) Calcd. (%): C, 66.87; H, 7.54; N, 3.12; S, 7.14 Found (%): C, 66.90; H, 7.50; N, 3.23; S, 7.05

Table 46

Compound No.	Physical property
IIc-21	mp 183-185 °C; ^{1}H-NMR (d_6-DMSO) δ 0.84 (1H, d, J = 9.6 Hz), 1.11 (3H, s), 1.18 (3H, s), 1.22-1.60 (7H, m), 1.93 (1H, m), 2.10-2.34 (6H, m), 3.41 (2H, t, J = 6.3 Hz), 3.92 (2H, s), 3.97 (1H, m), 6.79 (1H, d, J = 7.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.77 (1H, d, J = 7.8 Hz), 7.97 (1H, d, J = 6.9 Hz), 8.18 (1H, s), 10.39 (1H, br), 12.53 (1H, br); IR (Nujol) 3425, 3303, 3093, 2598, 1729, 1604, 1574, 1522, 1469, 1282, 1230, 1122 cm^{-1}; $[\alpha]_D^{27}$ +32.1±0.7° (c=1.000, MeOH); Anal. ($C_{24}H_{31}NO_5S\cdot0.4H_2O$) Calcd. (%): C, 63.66; H, 7.08; N, 3.09; S, 7.08 Found (%): C, 63.79; H, 7.14; N, 3.15; S, 7.06
IIc-22	^{1}H-NMR ($CDCl_3$) δ 0.93 (1H, d, J = 10.2 Hz), 1.10 (3H, s), 1.23 (3H, s), 1.38-1.92 (8H, m), 1.99 (1H, m), 2.16-2.38 (3H, m), 3.46 (2H, t, J = 6.3 Hz), 3.95 (2H, s), 4.32 (1H, m), 6.32 (1H, d, J = 9.0 Hz), 6.96 (1H, dd, J = 2.1, 9.0 Hz), 7.24 (1H, t, J = 2.1 Hz), 7.51 (1H, s), 8.04 (1H, d, J = 9.0 Hz); IR (KBr) 3359, 1734, 1603, 1523, 1469, 1236, 1128 cm^{-1}; $[\alpha]_D^{26}$ +26.8±0.7° (c=1.015, MeOH); Anal. ($C_{24}H_{31}NO_5S\cdot0.4H_2O$) Calcd. (%): C, 63.66; H, 7.08; N, 3.09; S, 7.08 Found (%): C, 63.64; H, 7.13; N, 3.07; S, 6.99
IIc-23	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.5 Hz), 1.12 (3H, s), 1.24 (3H, s), 1.38-2.40 (12H, m), 3.47 (2H, t, J = 6.6 Hz), 3.97 (2H, s), 4.33 (1H, m), 5.36 (2H, br s), 6.28 (1H, d, J = 9.0 Hz), 7.00 (1H, dd, J = 2.1, 8.7 Hz), 7.65 (1H, d, J = 8.7 Hz), 7.71 (1H, s), 7.98 (1H, d, J = 2.1 Hz); IR ($CHCl_3$) 3438, 3238, 1730, 1637, 1601, 1518, 1436, 1124 cm^{-1}; $[\alpha]_D^{24}$ +23.7±0.6° (c=1.004, MeOH); Anal. ($C_{24}H_{31}NO_5S\cdot0.5H_2O$) Calcd. (%):C, 63.41; H, 7.10; N, 3.08; S, 7.05 Found (%):C, 63.40; H, 6.98; N, 3.25; S, 7.09
IIc-24	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.5 Hz), 1.16 (3H, s), 1.20 (3H, s), 1.40-1.92 (8H, m), 2.04 (1H, m), 2.18-2.42 (3H, m), 3.55 (2H, t, J = 6.3 Hz), 4.04 (2H, s), 4.30 (1H, m), 6.55 (1H, d, J = 8.7 Hz), 6.93 (1H, dd, J = 2.4, 6.6 Hz), 7.32 (1H, d, J = 2.4 Hz), 7.33 (1H, d, J = 6.6 Hz), 7.67 (1H, s), 12.10 (1H, s); IR ($CHCl_3$) 3508, 3450, 2684, 1780, 1732, 1624, 1585, 1562, 1523, 1456, 1269 cm^{-1}; $[\alpha]_D^{27}$ +28.4±0.7° (c=1.000, MeOH); Anal. ($C_{24}H_{31}NO_5S\cdot0.5H_2O$) Calcd. (%): C, 63.41; H, 7.10; N, 3.08; S, 7.05 Found (%): C, 63.48; H, 6.98; N, 3.16; S, 6.98
IIc-27	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.17-2.41 (3H, m), 3.53 (2H, t, J = 6.6 Hz), 4.03 (2H, s), 4.32 (1H, m), 6.18 (1H, d, J = 8.7 Hz), 7.21 (1H, dt, J = 2.4, 9.0 Hz), 7.53 (1H, dd, J = 2.4, 8.4 Hz), 8.33 (1H, dd, J = 5.1, 9.0 Hz); IR ($CHCl_3$) 3508, 3442, 1780, 1732, 1651, 1603, 1516, 1468, 1244, 1122 cm^{-1}; $[\alpha]_D^{25}$ +29.2±0.7° (c=1.006, MeOH); Anal. ($C_{24}H_{30}FNO_4S\cdot0.3H_2O$) Calcd. (%): C, 63.64; H, 6.81; F, 4.19; N, 3.09; S, 7.08 Found (%):C, 63.65; H, 6.76; F, 4.10; N, 3.14; S, 7.16

Table 47

Compound No.	Physical property
IIc-28	mp 144-146 °C; ^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.5 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.17-2.41 (3H, m), 3.52-3.57 (2H, m), 4.03 (2H, s), 4.33 (1H, m), 6.16 (1H, d, J = 8.4 Hz), 7.17 (1H, dt, J = 2.7, 8.7 Hz), 7.78 (1H, dd, J = 5.1, 8.7 Hz), 8.06 (1H, dd, J = 2.7, 9.9 Hz) ; IR (Nujol) 3286, 2538, 1722, 1608, 1552, 1244, 1136 cm^{-1}; $[\alpha]_D^{25}$ +27.3±0.7° (c=1.009, MeOH); Anal. ($C_{24}H_{30}FNO_4S$) Calcd. (%): C, 64.41; H, 6.76; F, 4.24; N, 3.13; S, 7.16 Found (%): C, 64.23; H, 6.84; F, 4.16; N, 3.19; S, 7.12
IIc-34	mp 95-96 °C; ^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.5 Hz), 1.17 (3H, s), 1.24 (3H, s), 1.40-1.96 (8H, m), 2.02 (1H, m), 2.18-2.41 (3H, m), 3.47-3.58 (2H, m), 4.01 (2H, s), 4.40 (1H, m), 6.50 (1H, d, J = 8.7 Hz), 7.38 (1H, d, J = 5.7 Hz), 7.43 (1H, d, J = 7.8 Hz), 7.55 (1H, d, J = 7.8 Hz), 7.59 (1H, d, J = 5.7 Hz), 7.96 (1H, dd, J = 1.2, 7.8 Hz) ; IR (Nujol) 3265, 2544, 1728, 1608, 1577, 1550, 1319, 1240, 1225, 1128, 1111 cm^{-1}; $[\alpha]_D^{25}$ +45.6±0.9° (c=1.006, MeOH); Anal. ($C_{24}H_{31}NO_4S$) Calcd. (%): C, 67.10; H, 7.27; N, 3.26; S, 7.46 Found (%): C, 66.88; H, 7.14; N, 3.34; S, 7.43
IIc-39	^{1}H-NMR ($CDCl_3$) δ 0.99 (1H, d, J = 10.2 Hz), 1.17 (3H, s), 1.24(3H, s), 1.44-1.94 (8H, m), 2.02 (1H, m), 2.18-2.40 (3H, m), 3.53 (2H, t, J = 6.3 Hz), 3.98 (3H, s), 4.01 (2H, s), 4.40 (1H, m), 6.43 (1H, s), 6.49 (1H, d, J = 8.7 Hz), 7.42 (1H, t, J = 7.5 Hz), 7.58 (1H, dd, J = 0.9, 7.5 Hz), 7.93 (1H, dd, J = 0.9, 7.5 Hz); IR ($CHCl_3$) 3455, 1780, 1732, 1649, 1508, 1373, 1205, 1151 cm^{-1}; $[\alpha]_D^{24}$ +41.7±0.8° (c=1.007, MeOH); Anal. ($C_{25}H_{33}NO_5S\cdot0.2H_2O$) Calcd. (%): C, 64.82; H, 7.27; N, 3.02; S, 6.92 Found (%): C, 64.85; H, 7.30; N, 3.10; S, 6.64
IIc-41	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 9.9 Hz), 1.19 (3H, s), 1.25 (3H, s), 1.46-1.96 (8H, m), 2.03 (1H, m), 2.22-2.41 (3H, m), 3.53 (2H, t, J = 6.3 Hz), 4.00 (2H, s), 4.43 (1H, m), 6.53 (1H, d, J = 9.3 Hz), 7.44-7.56 (3H, m), 7.66 (1H, d, J = 6.3 Hz), 7.91 (1H, m), 8.18 (1H, m), 8.30 (1H, d, J = 7.5 Hz); IR ($CHCl_3$) 3454, 1780, 1731, 1649, 1512, 1444, 1217, 1122 cm^{-1}; $[\alpha]_D^{25}$ +45.4±0.8° (c=1.013, MeOH); Anal. ($C_{28}H_{33}NO_4S\cdot0.3H_2O$) Calcd. (%): C, 69.34; H, 6.98; N, 2.89; S, 6.61 Found (%): C, 69.21; H, 7.01; N, 3.04; S, 6.59
IIc-49	^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 9.9 Hz), 1.17 (3H, s), 1.25 (3H, s), 1.49-2.39 (12H, m), 3.45 (2H, s), 3.51 (2H, t, J = 6.3 Hz), 4.00 (3H, s), 4.37 (1H, m), 4.79 (2H, s), 6.20 (1H, d, J = 9.3 Hz), 7.32-7.40 (2H, m), 7.74 (1H, dd, J = 7.2, 1.5 Hz), 8.16 (1H, s); IR ($CHCl_3$) 3444, 2829, 1733, 1650, 1573, 1508, 1471, 1425, 1384, 1367, 1214 cm^{-1}; $[\alpha]_D^{24.0}$ +24.8±0.6° (c=1.020, MeOH); Anal. ($C_{26}H_{35}NO_6$ $0.5H_2O$) Calcd. (%): C, 66.93, H, 7.78; N, 3.00Found (%): C, 66.85; H, 7.78; N, 3.10

Table 48

Compound No.	Physical property
IIc-51	^{1}H-NMR ($CDCl_3$) δ 0.93 (1H, d, J = 9.9 Hz), 1.14 (3H, s), 1.23 (3H, s), 1.41-1.90 (8H, m), 2.00 (1H, m), 2.17-2.38 (3H, m), 3.49 (2H, t, J = 6.3 Hz), 3.99 (2H, s), 4.29 (1H, m), 6.27 (1H, d, J = 9.0Hz), 6.89 (1H, dd, J = 2.1, 8.7 Hz), 6.99 (1H, d, J = 2.1 Hz), 7.56 (1H, d, J = 8.7 Hz), 8.00 (1H, s); IR (KBr) 3475, 1734, 1626, 1560, 1518, 1493, 1471, 1441, 1385, 1367, 1265, 1221, 1122 cm^{-1}; $[\alpha]_D^{27}$ +22.3±0.6° (c=1.000, MeOH); Anal. ($C_{24}H_{31}NO_6\cdot0.5H_2O$) Calcd. (%): C, 65.74; H, 7.35; N, 3.19Found (%): C, 65.79; H, 7.43; N, 3.36
IIc-52	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.5 Hz), 1.13 (3H, s), 1.24 (3H, s), 1.48-1.90 (8H, m), 2.01 (1H, m), 2.18-2.40 (3H, m), 3.49 (2H, t, J = 6.5 Hz), 3.95 (1H, d, J = 16.5 Hz), 4.02 (1H, d, J = 16.5 Hz), 4.32 (1H, m), 6.12 (1H, d, J = 9.0 Hz), 6.91(1H, dd, J = 2.7, 9.0Hz), 7.36 (1H, d, J = 9.0 Hz), 7.52 (1H, d, J = 9.0 Hz), 7.98 (1H, s); IR ($CHCl_3$) 3442, 3265, 1730, 1643, 1620, 1558, 1514, 1468, 1385, 1367, 1190, 1167, 1136 cm^{-1}; $[\alpha]_D^{27}$ +21.6±0.6° (c=1.006, MeOH); Anal. ($C_{24}H_{31}NO_6\cdot0.5H_2O$) Calcd. (%): C, 65.74; H, 7.35; N, 3.19 Found (%): C, 65.80; H, 7.46; N, 3.34

Table 48 (continued)

Compound No.	Physical property
IIc-56	^{1}H-NMR ($CDCl_3$) δ 0.99 (1H, d, J = 10.2 Hz), 1.25 (6H, s), 1.47-1.79 (7H, m), 1.92-2.05 (2H, m), 2.19 (1H, m), 2.25-2.39 (2H, m), 3.51 (2H, t, J = 6.3 Hz), 3.96(1H, d, J = 16.2 Hz), 4.00 (1H, d, J = 16.2 Hz), 4.46 (1H, m), 6.89 (1H, d, J = 2.1 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.69 (1H, d, J = 2.1 Hz), 7.74 (1H, dd, J = 1.2, 7.8 Hz), 7.88 (1H, d, J = 9.3 Hz), 8.13 (1H, dd, J = 1.2, 7.8 Hz); IR ($CHCl_3$) 3435, 2665, 2573, 2474, 1780, 1732, 1651, 1606, 1595, 1547, 1535, 1473, 1421, 1367, 1352, 1325, 1296, 1167, 1120 cm^{-1}; $[\alpha]_D^{25.5}$ +14.7±0.5° (c=1.007, MeOH); Anal. ($C_{24}H_{31}NO_5 \cdot 0.3H_2O$) Calcd. (%): C, 68.81; H, 7.60; N, 3.34 Found (%): C, 68.71; H, 7.60; N, 3.44
IIc-65	mp 191-192 °C; ^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.5 Hz), 1.15 (3H, s), 1.25 (3H, s), 1.46-1.88 (8H, m), 2.01 (1H, m), 2.11 (1H, m), 2.21-2.37 (2H, m), 3.51-3.58 (2H, m), 4.07 (2H, s), 4.30 (1H, m), 6.21 (1H, d, J = 9.3 Hz), 6.68 (1H, d, J = 1.2 Hz), 6.99 (1H, d, J = 5.4 Hz), 7.23 (1H, dd, J = 0.6, 5.4 Hz), 11.27 (1H, s) ; IR (KBr) 3433, 3276, 2663, 2534, 1736, 1591, 1541, 1508, 1473, 1458, 1244, 1228, 1211, 1151 cm^{-1}; $[\alpha]_D^{25}$ +18.0±06° (c=1.008, MeOH); Anal. ($C_{22}H_{30}N_2O_4S \cdot 0.1H_2O$) Calcd. (%): C, 62.86; H, 7.24; N, 6.66; S, 7.63 Found (%): C, 62.81; H, 7.30; N, 6.80; S, 7.47
IIc-66	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.24 (3H, s), 1.46-1.88 (8H, m), 2.01 (1H, m), 2.14 (1H, m), 2.21-2.37 (2H, m), 3.53 (2H, t, J = 6.6 Hz), 4.07 (2H, s), 4.29 (1H, m), 6.20 (1H, d, J = 9.3 Hz), 6.64 (1H, d, J = 2.1 Hz), 6.86 (1H, d, J = 5.4 Hz), 6.92 (1H, d, J = 5.4 Hz), 11.06 (1H, s) ; IR ($CHCl_3$) 3448, 3209, 1726, 1631, 1543, 1518, 1126 cm^{-1}; $[\alpha]_D^{25}$ +14.4±0.5° (c=1.007, MeOH); Anal. ($C_{22}H_{30}N_2O_4S \cdot 0.4H_2O$) Calcd. (%): C, 62.06; H, 7.29; N, 6.58; S, 7.53Found (%): C, 62.02; H, 7.31; N, 6.67; S, 7.56

Table 49

Compound No.	Physical property
IIc-81	^{1}H-NMR ($CDCl_3$) δ 0.92 (1H, d, J = 10.2 Hz), 1.09 (3H, s), 1.20 (3H, s), 1.41-1.73 (7H, m), 1.82 (1H, m), 1.96 (1H, br s), 2.14- 2.35 (3H, m), 2.41 (3H, s), 3.46 (2H, t, J = 6.3 Hz), 3.98 (2H, s), 4.27 (1H, m). 6.22 (1H, d, J = 9.0 Hz), 6.72 (1H, d, J = 2.1 Hz), 7.24 (1H, d, J = 2.1 Hz), 8.03 (1H, s); IR ($CHCl_3$) 3599, 3442, 3265, 2565, 1730, 1645, 1608, 1570, 1514, 1460, 1417, 1385, 1367, 1329, 1286, 1240, 1137 cm^{-1}; $[\alpha]_D^{24}$ +24.2±0.6° (c=1.014, MeOH) Anal. ($C_{25}H_{33}NO_6 \cdot 0.4H_2O$) Calcd. (%): C, 66.62; H, 7.55; N, 3.10 Found (%): C, 66.66; H, 7.47; N, 3.29
IIc-84	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.2 Hz), 1.12 (3H, s), 1.25 (3H, s), 1.34 (2H, t, J = 7.5 Hz), 1.44-2.41 (10H, m), 3.56 (2H, br t, J = 5.4 Hz), 4.04 (2H, br s), 4.22-4.40 (3H, m), 6.22 (1H, d, J = 9.0 Hz), 7.65 (1H, dd, J = 1.5, 8.7 Hz), 7.77 (1H, d, J = 8.7 Hz), 7.78 (1H, br s), 8.22 (1H, br s); IR ($CHCl_3$) 3437, 2924, 1730, 1651, 1514, 1441, 1319 cm^{-1}; $[\alpha]_D^{24}$ +20.9±0.6° (c=1.010%, MeOH); Anal. ($C_{27}H_{36}N_2O_6S \cdot 0.4H_2O$) Calcd. (%): C, 61.90; H, 7.08; N, 5.35; S, 6.12 Found (%): C, 61.82; H, 6.85; N, 5.30; S, 6.09
IIc-86	^{1}H-NMR (d_6-DMSO) δ 0.85 (1H, d, J = 8.7 Hz), 1.11 (3H, s), 1.18 (3H, s), 1.27-2.38 (12H, m), 3.41 (2H, t, J = 6.3 Hz), 3.73 (2H, s), 3.97 (1H, m), 5.83 (2H, br s), 7.61 (1H, dd, J = 2.1, 8.7 Hz), 7.83 (1H, d, J = 8.7 Hz), 7.98 (1H, d, J = 6.6 Hz), 8.18 (1H, br s), 8.28 (1H, d, J = 2.1 Hz), 8.73 (1H, s), 12.54 (1H, br s); IR (Nujol) 3334 2923, 1676, 1633, 1571, 1523, 1442, 1377, 1244, 1126 cm^{-1}; $[\alpha]_D^{24}$ +19.1±0.6° (c=1.018%, MeOH); Anal. ($C_{25}H_{33}N_3O_5S \cdot 0.4H_2O$) Calcd. (%): C, 60.68; H, 6.88; N, 8.49; S, 6.48 Found (%): C, 60.73; H, 6.86; N, 8.67; S, 6.41
IIc-94	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.2 Hz), 1.15 (3H, s), 1.26 (3H, s), 1.48-1.91 (8H, m), 2.02 (1H, m), 2.06 (3H, s), 2.18-2.40 (3H, m), 3.51 (2H, t, J = 6.3 Hz), 3.90 and 3.97 (each 1H, ABq, J = 16.2 Hz), 4.36 (1H, m), 4.49 (1H, dd, J = 6.3, 15.0 Hz), 4.61 (1H, dd ,J = 6.3, 15.0 Hz), 6.27 (1H, br d, J = 9.0 Hz), 6.41 (1H, br s), 7.33 (1H, br d, J = 8.7 Hz), 7.76 (1H, s), 7.79 (1H, d, J = 8.7 Hz), 8.29 (1H, br s); IR ($CHCl_3$) 3444, 1733, 1653, 1516, 1471, 1435, 1367, 1240, 1130 cm^{-1}; $[\alpha]_D^{24}$ +23.2±0.6° (c=1.015, MeOH) Anal. ($C_{27}H_{36}N_2O_5S \cdot 0.3H_2O$) Calcd. (%): C, 64.08; H, 7.29; N, 5.54; S, 6.34 Found (%): C, 63.99; H, 7.24; N, 5.46; S, 6.35

Table 49 (continued)

Compound No.	Physical property
IIc-95	mp 133-134 °C; ^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ 0.96 (1H, d, J = 9.9 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.26 (3H, t, J = 7.5 Hz), 1.42-2.03 (9H, m), 2.22-2.39 (3H, m), 3.52 (2H, t, J = 6.6 Hz), 3.99 (2H, s), 4.14 (2H, q, J = 7.5 Hz), 4.29 (1H, m), 4.49 (2H, br s), 5.50 (1h, br s), 6.34 (1H, br d, J = 8.7 Hz), 7.38 (1H, d, J = 8.1 Hz), 7.82 (1H, d, J = 8.1 Hz), 7.84 (1H, br s), 8.30 (1H, s); IR ($CHCl_3$) 3446, 1722, 1653, 1514, 1471, 1435, 1385, 1238, 1132, 1061 cm^{-1}; $[\alpha]_D^{23}$ +22.9±0.6° (c=1.013, MeOH) Anal. ($C_{28}H_{38}N_2O_6S$) Calcd. (%): C, 63.37; H, 7.22; N, 5.28; S, 6.04 Found (%): C, 63.18; H, 7.14; N, 5.23; S, 5.95

Table 50

Compound No.	Physical property
IIc-96	^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.5 Hz), 1.16 (3H, s), 1.26 (3H, s), 1.47-1.72 (7H, m), 1.86 (1H, m), 2.02 (1H, m), 2.18-2.39 (3H, m), 2.92 (3H, s), 3.51 (2H, m), 3.96 and 4.03 (each 1H, ABq, J = 16.5 Hz), 4.36 (1H, m), 4.44 (2H, br s), 5.75 (1H, br s), 6.24 (1H, br d, J = 8.7 Hz), 7.41 (1H, br d, J = 8.1 Hz), 7.76 (1H, s), 7.83 (1H, d, J = 8.1 Hz), 8.42 (1H, br s); IR ($CHCl_3$) 3442, 1734, 1649, 1516, 1496, 1471, 1437, 1327, 1223, 1149, 1074 cm^{-1}; $[\alpha]_D^{26}$ +19.2±0.6° (c=1.010, MeOH) Anal. ($C_{26}H_{36}N_2O_6S_2 \cdot 0.4H_2O$) Calcd. (%): C, 57.41; H, 6.82; N, 5.15; S, 11.79 Found (%): C, 57.36; H, 6.65; N, 5.02; S, 11.65
IIc-97	^{1}H-NMR ($CDCl_3$) 6 0.96 (1H, d, J = 10.2 Hz), 1.13 (3H, s), 1.24 (3H, s), 1.48-1.72 (7H, m), 1.89 (1H, m), 2.00 (1H, m), 2.16-2.38 (3H, m), 3.49 (2H, t, J = 6.6 Hz), 3.89 and 3.96 (each 1H, ABq, J = 16.5 Hz), 4.25 (1H, br d, J = 15.0 Hz), 4.32 (1H, m), 4.46 (1H, br d, J = 15.0 Hz), 6.37 (1H, d, J = 8.4 Hz), 7.21 (1H, dd, J = 1.2, 8.7 Hz), 7.71 (1H, d, J = 8.7 Hz), 7.74 (1H, s), 8.21 (1H, br s); IR ($CHCl_3$) 3440, 1720, 1645, 1601, 1518, 1471, 1437, 1240, 1215, 1132 cm^{-1}; $[\alpha]_D^{25}$ +23.7±0.6° (c=1.009, MeOH) Anal. ($C_{26}H_{35}N_3O_5S \cdot 0.5H_2O$) Calcd. (%): C, 61.15; H, 7.11; N, 8.23; S, 6.28 Found (%): C, 61.02; H, 6.81; N, 8.14; S, 6.30
IIc-99	mp 164-166 °C; ^{1}H-NMR (d_6-DMSO) δ 0.85 (1H, d, J = 9.6 Hz), 1.12 (3H, s), 1.19 (3H, s), 1.24-2.37 (12H, m), 3.41 (2H, t, J = 6.3 Hz), 3.92 (2H, s), 3.99 (1H, m), 7.38 (1H, br s), 7.87 (1H, dd, J = 2.1, 8.7 Hz), 8.05-8.13 (3H, m), 8.32 (1H, s), 8.82 (1H, d, J = 1.2 Hz); IR (Nujol) 3448, 3356, 3211, 2925, 1718, 1691, 1639, 1520, 1462, 1402, 1254, 1144 cm^{-1}; $[\alpha]_D^{25}$ +28.4±0.7° (c=1.008%, MeOH); Anal. ($C_{25}H_{32}N_2O_5S \cdot 0.2H_2O$) Calcd. (%): C, 63.05; H, 6.86; N, 5.88; S, 6.73 Found (%): C, 63.01; H, 6.78; N, 5.84; S, 6.70
IIc-115	^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.25 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.18-2.41 (3H, m), 2.46 (3H, s), 2.53 (3H, s), 3.47-3.58 (2H, m), 4.02 (2H, s), 4.35 (1H, m), 6.22 (1H, d, J = 8.4 Hz), 7.05 (1H, s), 7.83 (1H, s), 7.93 (1H, s) ; IR ($CHCl_3$) 3508, 3440, 1780, 1732, 1649, 1514, 1242, 1126 cm^{-1}; $[\alpha]_D^{25}$ +30.4±0.7° (c=1.017, MeOH) Anal. ($C_{26}H_{35}NO_4S \cdot 0.2H_2O$) Calcd. (%): C, 67.71; H, 7.74; N, 3.01; S, 6.95 Found (%): C, 67.37; H, 7.91; N, 2.95; S, 6.79
IIc-128 -	^{1}H-NMR ($CDCl_3$) 6 0.99 (1H, d, J = 10.5 Hz), 1.12 (3H, s), 1.25 (each 3H, s), 1.41-2.41 (12H, m), 3.49 (2H, t, J = 7.5 Hz), 3.99 (2H, s), 4.32 (2H, s), 5.05 (2H, br s), 6.29 (1H, d, J = 9.0 Hz), 7.48 (1H, d, J = 10.2 Hz), 7.67 (1H, s), 8.09 (1H, d, J = 8.7 Hz); IR (CHCl3) 3579, 3438, 3192, 2924, 1730, 1635, 1518, 1433, 1277 cm^{-1}, $[\alpha]_D^{26}$ +22.4±0.6° (c=1.014%, MeOH); Anal. ($C_{24}H_{30}NO_5SF \cdot 0.6H_2O$) Calcd. (%): C, 60.77; H, 6.63; N, 2.95; S, 6.76; F, 4.00 Found (%): C, 60.72; H, 6.35; N, 2.85; S, 6,58; F, 4.01

Table 51

Compound No.	Physical property
IIc-129	^{1}H-NMR ($CDCl_3$) δ 0.97 (1H, d, J = 10.5 Hz), 1.15 (3H, s), 1.25 (3H, s), 1.44-2.40 (12H, m), 3.55 (2H, t, J = 6.3 Hz), 3.98 (3H, s), 4.02 (2H, s), 4.32 (1H, m), 6.19 (1H, d, J = 6.6 Hz), 7.62 (1H, d, J = 10.5 Hz), 7.69 (1H, s), 8.07 (1H, d, J = 8.1 Hz); IR ($CHCl_3$) 3444, 2924, 1780, 1732, 1649, 1512, 1466, 1415, 1263, 1225 cm^{-1}; $[\alpha]_D^{25}$ +22.5±0.6° (c=1.006%, MeOH); Anal. ($C_{25}H_{32}NO_5SF \cdot 0.2H_2O$) Calcd. (%): C, 62.40; H, 6.79; N, 2.91; S, 6.66; F, 3.95 Found (%): C, 62.32; H, 6.74; N, 2.86; S, 6.72; F, 3.88
IIc-135	^{1}H-NMR ($CDCl_3$-DMSO-d_6) δ 0.93 (1H, d, J = 10.2 Hz), 1.16 (3H, s), 1.23 (3H, s), 1.42-1.74 (7H, m), 1.91-2.02 (2H, m), 2.20-2.36 (3H, m), 3.52 (2H, t, J = 6.9 Hz), 4.00 (2H, s), 4.27 (1H, m), 6.34 (1H, br d, J = 8.4 Hz), 7.35 (1H, dd, J = 2.1, 8.7 Hz), 7.42 (1H, d, J = 8.7 Hz), 7.96 (1H, d, J = 2.1 Hz), 8.11 (1H, s); IR (nujol) 3440, 1724, 1635, 1556, 1298, 1252, 1173, 1128 cm^{-1}; $[\alpha]_D^{24}$ +17.1 ±0.6° (c=1.004, MeOH)
IIe-04	mp 79-81 °C; ^{1}H-NMR ($CDCl_3$) δ 0.95 (1H, d, J = 9.9 Hz), 1.21 (3H, s), 1.23 (3H, s), 1.36-1.88 (8H, m), 2.00 (1H, m), 2.10-2.38 (3H, m), 2.65 (2H, t, J = 6.9 Hz), 3.17 (1H, d, J = 14.7 Hz), 3.22 (1H, d, J = 14.7 Hz), 4.27 (1H, m), 6.18 (1H, d, J = 9.0 Hz), 7.32-7.36 (2H, m), 7.86 (1H, dd, J = 1.5, 2.4 Hz); IR (Nujol) 3396, 3361, 3109, 3076, 2617, 1720, 1631, 1593, 1543, 1508, 1234, 1221, 1124 cm^{-1}; $[\alpha]_D^{26}$ +29.4±0.7° (c=1.005, MeOH); Anal. ($C_{20}H_{29}NO_3S_2$) Calcd. (%): C, 60.72; H, 7.39; N, 3.54; S, 16.21 Found (%): C, 60.73; H, 7.45; N, 3.61; S, 16.17
IIe-17	mp 176-178 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 9.9 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.18-2.41 (3H, m), 2.66 (2H, t, J = 6.9 Hz), 3.15 (1H, d, J = 14.7 Hz), 3.21 (1H, d, J = 14.7 Hz), 4.36 (1H, m), 6.24 (1H, d, J = 8.7 Hz), 7.40 (1H, dt, J = 1.2, 7.5 Hz), 7.45 (1H, dt, J = 1.2, 7.5 Hz), 7.85 (1H, s), 7.87 (1H, dd, J = 1.2, 7.5 Hz), 8.30 (1H, dd, 1.2, 7.5 Hz); IR (Nujol) 3425, 3091, 3059, 2632, 1726, 1608, 1522, 1261, 1250, 1215, 1126 cm^{-1}; $[\alpha]_D^{26}$ +34.0±0.7° (c=1.002, MeOH); Anal. ($C_{24}H_{31}NO_3S_2$) Calcd. (%): C, 64.68; H, 7.01; N, 3.14; S, 14.39 Found (%): C, 64.48; H, 7.01; N, 3.15; S, 14.25
IIe-20	mp 117-118 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.5 Hz), 1.14 (3H, s), 1.26 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.18-2.42 (3H, m), 2.49 (3H, s), 2.66 (2H, t, J = 6.9 Hz), 3.16 (1H, d, J = 14.7 Hz), 3.21 (1H, d, J = 14.7 Hz), 4.35 (1H, m), 6.23 (1H, d, J = 8.7 Hz), 7.23 (1H, dd, J = 1.2, 8.4 Hz), 7.74 (1H, d, J = 8.4 Hz), 7.82 (1H, s), 8.11 (1H, d, J = 1.2 Hz; IR (Nujol) 3348, 1726, 1597, 1537, 1255, 1219 cm^{-1}; $[\alpha]_D^{26}$ +31.9±0.7° (c=1.002, MeOH); Anal. ($C_{25}H_{33}NO_3S_2$) Calcd. (%): C, 65.32; H, 7.24; N, 3.05; S, 13.95 Found (%): C, 65.15; H, 7.05; N, 3.10; S, 13.93
IIe-21	mp 170-172 °C; ^{1}H-NMR (d_6-DMSO) δ 0.84 (1H, d, J = 9.9 Hz), 1.11 (3H, s), 1.18 (3H, s), 1.28-1.60 (7H, m), 1.94 (1H, m), 2.12-2.34 (6H, m), 2.55 (2H, t, J = 7.2 Hz), 3.17 (2H, s), 3.97 (1H, m), 6.79 (1H, d, J = 7.8 Hz), 7.24 (1H, t, J = 7.8 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.98 (1H, d, J = 6.6 Hz), 8.18 (1H, s), 10.39 (1H, br), 12.46 (1H, br); IR (Nujol) 3357, 3246, 32613, 1693, 1595, 1574, 1541. 1469, 1296, 1228 cm^{-1}; $[\alpha]_D^{27}$ +38.7±0.8° (c=1.004, MeOH); Anal. ($C_{24}H_{31}NO_4S_2$) Calcd. (%): C, 62.44; H, 6.77; N, 3.03; S, 13.89 Found (%): C, 62.25; H, 6.86; N, 3.08; S, 13.60

Table 52

Compound No.	Physical property
IIe-22	^{1}H-NMR ($CDCl_3$) δ 0.93 (1H, d, J = 10.2 Hz), 1.10 (3H, s), 1.23 (3H, s), 1.36-1.92 (8H, m), 1.99 (1H, m), 2.16-2.39 (3H, m), 2.56 (2H, t, J = 7.2 Hz), 3.13 (2H, s), 4.32 (1H, m), 6.35 (1H, d, J = 9.0 Hz), 6.95 (1H, dd, J = 2.1, 9.0 Hz), 7.24 (1H, t, J = 2.1 Hz), 7.51 (1H, s), 8.03 (1H, d, J = 9.0 Hz); IR (KBr) 3361, 2661, 1707, 1603, 1523, 1468, 1236 cm^{-1}; $[\alpha]_D^{26}$ +23.2±0.6° (c=1.015, MeOH); Anal. ($C_{24}H_{31}NO_4S_2 \cdot 0.4H_2O$) Calcd. (%): C, 61.48; H, 6.84; N, 2.99; S, 13.68 Found (%): C, 61.51; H, 6.74; N, 3.01; S, 13.67

Table 52 (continued)

Compound No.	Physical property
IIe-24	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.5 Hz), 1.15 (3H, s), 1.26 (3H, s), 1.40-1.92 (8H, m), 2.03 (1H, m), 2.18-2.42 (3H, m), 2.64 (2H, t, J = 7.2 Hz), 3.19 (2H, s), 4.29 (1H, m), 6.59 (1H, d, J = 8.4 Hz), 6.92 (1H, dd, J = 2.1, 6.6 Hz), 7.31 (1H, t, J = 2.1 Hz), 7.32 (1H, t, J = 6.6 Hz), 7.69 (1H, s), 12.22 (1H, s); IR ($CHCl_3$) 3508, 3452, 2683, 1711, 1624, 1585, 1562, 1523, 1456, 1271, 1227, 1217, 1205 cm^{-1}; $[\alpha]_D^{26}$ +34.1±0.7° (c=1.005, MeOH); Anal. ($C_{24}H_{31}NO_4S$) Calcd. (%): C, 62.44; H, 6.77; N, 3.03; S, 13.89 Found (%): C, 62.48; H, 6.86; N, 3.03; S, 13.63
IIe-28	mp 197-199 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.5 Hz), 1.14 (3H, s), 1.25 (3H, s), 1.40-1.92 (8H, m), 2.02 (1H, m), 2.18-2.41 (3H, m), 2.66 (2H, t, J = 6.9 Hz), 3.16 (1H, d, J = 15.0 Hz), 3.21 (1H, d, J = 15.0 Hz), 4.33 (1H, m), 6.19 (1H, d, J = 9.3 Hz), 7.16 (1H, td, J = 2.4, 8.7 Hz), 7.78 (1H, dd, J = 4.8, 8.7 Hz), 7.88 (1H, s), 8.07 (1H, dd, J = 2.4, 10.2 Hz); IR (Nujol) 3423, 3087,2636, 1728, 1606, 1523, 1444, 1433, 1248, 1203, 1128 cm^{-1}; $[\alpha]_D^{26}$ +31.0±0.7° (c=1.013, MeOH); Anal. ($C_{24}H_{30}FNO_3S_2$·0.1AcOEt) Calcd. (%): C, 62.03; H, 6.57; F, 4.02; N, 2.96; S, 13.57 Found (%): C, 61.84; H, 6.48; F, 3.96; N, 2.98; S, 13.56
IIe-34	mp 143-144 °C; ^{1}H-NMR ($CDCl_3$) δ 0.98 (1H, d, J = 10.2 Hz), 1.17 (3H, s), 1.24 (3H, s), 1.40-1.96 (8H, m), 2.02 (1H, m), 2.19-2.41 (3H, m), 2.64 (2H, t, J = 7.2 Hz), 3.15 (1H, d, J = 15.0 Hz), 3.20 (1H, d, J = 15.0 Hz), 4.41 (1H, m), 6.53 (1H, d, J = 8.7 Hz), 7.38 (1H, d, J = 5.4 Hz), 7.43 (1H, t, J = 7.8, Hz), 7.43 (1H, t, J = 7.8 Hz), 7.55 (1H, dd, J = 1.2, 7.8 Hz), 7.59 (1H, d, 5.4 Hz), 7.96 (1H, dd, J = 1.2, 7.8 Hz); IR (Nujol) 3421, 3402, 2625, 1712, 1618, 1579, 1529, 1250, 1215, 1120 cm^{-1}; $[\alpha]_D^{26}$ +48.2±0.9° (c=1.016, MeOH); Anal. ($C_{24}H_{31}NO_3S_2$) Calcd. (%): C, 64.68; H, 7.01; N, 3.14; S, 14.39 Found (%): C, 64.49; H, 6.85; N, 3.16; S, 14.12
IIe-54	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 10.2 Hz), 1.14 (3H, s), 1.24 (3H, s), 1.41-2.40 (12H, m), 2.64 (1H, t, J = 7.2 Hz), 3.19 (2H, s), 4.33 (1H, m), 6.14 (1H, d, J = 8.7 Hz), 7.12 (1H, dt, J = 6.0, 2.4 Hz), 7.25 (1H, dd, J = 8.4, 2.4 Hz), 7.81 (1H, dd, J = 8.4, 6.0 Hz), 8.09 (1H, s) ; IR ($CHCl_3$) 3446, 2674, 1710, 1654, 1563, 1506, 1490, 1257, 1220, 1205 cm^{-1}; $[\alpha]_D^{26.0}$ +22.8±1.2° (c=0.510, MeOH); Anal. ($C_{24}H_{30}FNO_4S$·0.2H_2O) Calcd. (%): C, 63.89; H, 6.79; F, 4.21; N, 3.10; S, 7.11 Found (%): C, 63.83; H, 6.93; F, 4.02; N, 3.18; S, 7.15

Table 53

Compound No.	Physical property
IIf-28	^{1}H-NMR ($CDCl_3$) δ 0.96 (1H, d, J = 9.9 Hz), 1.13 (3H, s), 1.25 (3H, s), 1.42-1.86 (9H, m), 2.02 (1H, m), 2.20-2.39 (4H, m), 4.31 (1H, m), 6.01 (1H, d, J = 8.7 Hz), 7.16(1H, dt, J = 2.4, 9.0 Hz), 7.77 (1H, dd, J = 4.5, 9.0 Hz), 7.84 (1H, s), 8.08 (1H, dd, J = 2.4, 10.2 Hz); IR ($CHCl_3$) 3516, 3444, 1709, 1653, 1603, 1564, 1514, 1471, 1433, 1250, 1142 cm^{-1}; $[\alpha]_D^{25}$ +33.6±0.7° (c=1.007, MeOH) Anal. ($C_{23}H_{28}FNO_3S$·0.2H_2O) Calcd. (%): C, 65.60; H, 6.80; N, 3.33; F, 4.51; S, 7.61 Found (%): C, 65.70; H, 6.70; N, 3.28; F, 4.32; S, 7.56
IIf-84	^{1}H-NMR ($CDCl_3$) δ 0.95 (1H, d, J = 9.9 Hz), 1.10 (3H, s), 1.25 (3H, s), 1.32 (3H, t, J = 7.2 Hz), 1.44-1.86 (9H, m), 2.00 (1H, m), 2.21-2.39 (4H, m), 2.24 (2H, q, J = 7.2 Hz), 4.30 (1H, m), 6.15 (1H, m), 7.65 (1H, br d, J = 8.4 Hz), 7.76 (1H, d, J = 8.4 Hz), 7.78 (1H, s), 8.18 (1H, br s); IR ($CHCl_3$) 3510, 3437, 1713, 1651, 1606, 1570, 1514, 1441, 1319, 1225, 1207, 1169, 1155, 1080, 1066 cm^{-1}; $[\alpha]_D^{24}$ +26.3±0.7° (c=1.009, MeOH) Anal. ($C_{26}H_{34}N_2O_5S$·0.4H_2O) Calcd. (%): C, 63.24; H, 7.10; N, 5.67; S, 6.49 Found (%): C, 63.35; H, 6.88; N, 5.55; S, 6.34

[0085] The compounds prepared in Examples above were tested for determining the in vivo and in vitro activities according to the method as shown in Experimental examples below.

Experiment 1 Binding activity to PGD_2 Receptor

(1) Preparation of Human Platelet Membrane Fraction

[0086] Blood was collected using a plastic syringe containing 3.8 % sodium citrate from the vein of healthy volunteers (adult male and female), then put into a plastic test tube and mixed by slow-reversion. The sample was then centrifuged

at 1800 rpm, for 10 min at room temperature, and the supernatant containing PRP (platelet-rich plasma) was collected. The PRP was recentrifuged at 2300 rpm, for 22 min at room temperature to obtain platelets. The platelets were homogenized using a homogenizer (Ultra-Turrax) followed by centrifugation 3 times at 20,000 rpm, 10 min at 4 °C to obtain a platelet membrane fraction. After protein determination, the membrane fraction was adjusted to 2 mg/ml and preserved in a refrigerator at -80 °C until using for the binding test.

(2) Binding to PGD_2 Receptor

[0087] To a binding-reaction solution (50 mM Tris/HCl, pH 7.4, 5 mM $MgCl_2$) (0.2 ml) were added the human platelet membrane fraction (0.1 mg) and 5 nM [^{3}H]PGD_2 (115 Ci/mmol), and the mixture was reacted at 4 °C for 90 min. After the reaction, the mixture was filtered through a glass fiber filter paper and washed several times with cooled physiological saline, then the radioactivity retained on the filter paper was measured. The specific-binding ratio was calculated by subtracting the non-specific binding ratio which is the radioactivity similarly measured in the presence of 10 μM PGD_2 from the total binding. The inhibitory activity of each compound was expressed as the concentration required for 50 % inhibition (IC_{50}), which was determined by depicting a substitution curve by plotting the binding ratio (%) in the presence of each compound, where the binding ratio in the absence of a test compound is 100 %.

Experiment 2 Evaluation of Antagonistic Activity Against PGD_2 Receptor Using Human Platelet

[0088] Peripheral blood was collected from a healthy volunteer using a syringe in which 1/9 volume of a citric acid/dextrose solution was previously added. The sample was subjected to centrifugation at 1200 rpm for 10 min to obtain the supernatant (PRP: platelet rich plasma). The resultant PRP was washed 3 times with a washing buffer and the number of platelets was counted with a micro cell counter. A suspension adjusted to contain the platelets at a final concentration of 5 x 10^8/ml was warmed at 37 °C, then subjected to the pretreatment with 3-isobutyl-1-methylxanthine (0.5 mM) for 5 min. To the suspension was added a test compound diluted at various concentration, and 10 minutes later, 0.1 μM PGD_2 was added to induce the reaction 2 minutes later, hydrochloric acid was added to terminate the reaction. The platelet was destroyed with an ultrasonic homogenizer. After centrifugation, the cAMP in the supernatant was determined by radioimmunoassay. PGD_2 receptor antagonism of a drug was evaluated as follows: the inhibition rate regarding cAMP increased by the addition of PGD_2 was determined at each concentration, and the concentration of the drug required for 50 % inhibition (IC_{50}) was calculated.

[0089] The results of Experiment 1 and 2 are shown below.

Table 54

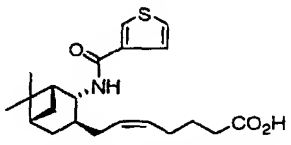
Compound No.	Binding activity to PGD_2 receptor in human platelet membrane fraction IC_{50}(μM)	Inhibitory activity for the increase of cAMP caused by PGD_2 in human platelet IC_{50}(μM)
Ia-17		0.011
Ia-20		0.017
Ia-65		0.018
Ic-22		0.010
Ic-23		0.01
Ic-52	0.074	0.01
IIa-4		0.019
IIa-17		0.015
IIa-22		0.0037
IIa-23	0.033	0.0025
IIa-28		0.016
IIa-34		0.014
IIa-52		0.0037
IIa-54		0.015
II a -66		0.017

Table 54 (continued)

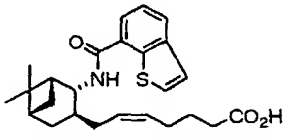
Compound No.	Binding activity to PGD_2 receptor in human platelet membrane fraction $IC_{50}(\mu M)$	Inhibitory activity for the increase of cAMP caused by PGD_2 in human platelet $IC_{50}(\mu M)$
IIc-4		0.018
IIc-17		0.0054
IIc-20		0.015
IIc-22		0.0046
IIc-23	0.0095	0.0049
IIc-24		0.013
IIc-28		0.013
IIc-34		0.011
IIc-52	0.0035	0.0082
IIc-81		0.008
IIc-86		0.008
IIc-96		0.017
IIc-97		0.011
IIc-99		0.006
IIc-128		0.005
IIc-129		0.018
IIc-135		0.003
IIe-22		0.0048
IIe-24		0.0057
IIe-28		0.017
IIe-34		0.019
IIf-84		0.020

Experiment 3 Change of plasma concentration of drug in rat

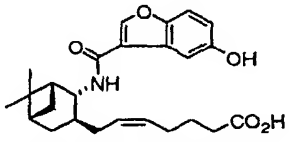
[0090] Compound (0.5 to 2 mg/kg) was administered intravenously to Jcl-SD male rats. The concentration of the unchanged compound was measured at 2, 5, 15, 30, 60, 120, and 240min after the administration by the use of HPLC (determination limit; 0.05 μg/ml) and LC/MS/MS (determination limit; 0.001 μg/ml) and the half life of the disappearance was calculated.



Reference compound 1



Reference compound 2



Reference compound 3

Table 55

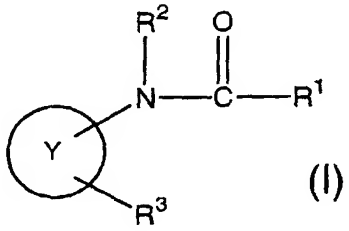
Compound No.	Half life of the disappearance (min)
Reference compound 1	8.0
IIa-4	21.6
IIc-4	44.3
IIe-4	40.0
Reference compound 2	17.0
IIa-34	34.6
IIc-34	66.7
Reference compound 3	8.7
IIa-52	16.7
IIc-52	23.4

Industrial Applicability

[0091] The compound of the present invention represented by the formula (I) having an antagonistic activity against PGD_2 receptor, is metabolically stable, and is useful in the improvement of conditions due to excessive production of PGD_2.

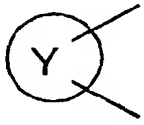
Claims

1. A compound represented by the formula (I):

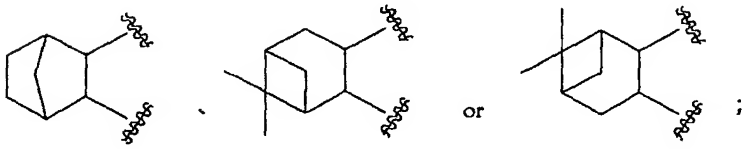


(I)

wherein

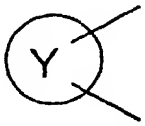


is

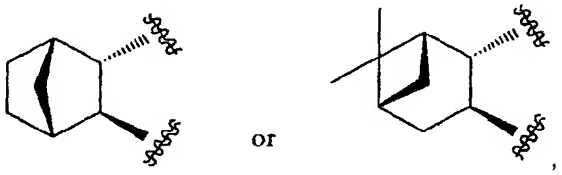


R^1 is optionally substituted heteroaryl;
R^2 is hydrogen or alkyl;
R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$;
R^4 is hydrogen or alkyl;
X^1 is -O- or -S-,
a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

2. A compound as described in Claim 1, wherein



is



a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

3. A compound as described in Claim 1 or Claim 2, wherein R^1 is optionally substituted thienyl, optionally substituted benzothienyl, optionally substituted furyl, optionally substituted benzofuryl, optionally substituted pyrrolyl, optionally substituted thienopyrrolyl or optionally substituted indolyl, a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

4. A compound as described in Claim 1 or Claim 2, wherein R^1 is heteroaryl which may be substituted with a group of the formula: $-Z^1-Z^2$ wherein Z^1 is a bond, -O-, -S-, -NH-, -NH-C(=O)-, -NH-C(=O)-O-, $-NH-SO_2-$,-C(=O)-, -O-C(=O)-, -C(=O)-O-, $-SO_2-$, $-CH_2-O-$, $-CH_2-NH-C(=O)-$, $-CH_2-NH-C(=O)-O-$, $-CH_2-NH-SO_2-$ or $-CH_2-C(=O)-$ and Z^2 is alkyl or optionally substituted amino; carboxy; halogen; hydroxy; or nitro, a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

5. A compound as described in any one of Claims 1 to 4, wherein R^3 is$-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$, $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$, $-CH_2-CH=CH-CH_2-X^1-CH_2-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-COOR^4$; R^4 is hydrogen; and X^1 is -O- or -S-, a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

6. A compound as described in Claim 5, wherein R^3 is $-CH_2-CH_2-CH_2-CH_2-CH=CH-COOR^4$ or $-CH_2-CH_2-CH_2-CH_2-X^1-CH_2-COOR^4$; R^4 is hydrogen; and X^1 is -O- or -S-, a prodrug, a pharmaceutically acceptable salt or a solvate thereof.

7. A pharmaceutical composition containing a compound, a prodrug, a pharmaceutically acceptable salt, or a solvate thereof as described in any one of Claims 1 to 6.

8. A pharmaceutical composition having an antagonistic activity against PGD_2 receptor as described in Claim 7.

9. A pharmaceutical composition as described in Claim 7, which is used for the treatment of nasal blockage.

10. A pharmaceutical composition as described in Claim 7, which is used for the treatment of allergic conjunctivitis.

11. A pharmaceutical composition as described in Claim 7, which is used for the treatment of allergic rhinitis.

12. A method for treating nasal blockage, allergic conjunctivitis or allergic rhinitis, which comprises administrating a composition as described in Claim 7.

13. Use of the compound as described in any one of Claims 1 to 6 for the preparation of a pharmaceutical composition for treating nasal blockage, allergic conjunctivitis or allergic rhinitis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09435

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D333/38, 333/54, 333/68, 333/62, 333/64, 333/76, 337/14, 307/68, 307/84, 307/85, 307/86, 307/91, 207/34, 209/42, 495/04, 209/42, 333/74, A61K31/381, 31/38, 31/341,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D333/38, 333/54, 333/68, 333/62, 333/64, 333/76, 337/14, 307/68, 307/84, 307/85, 307/86, 307/91, 207/34, 209/42, 495/04, 209/42, 333/74, A61K31/381, 31/38, 31/341,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA(STN),REGISTRY(STN),WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97/00853 A (Shionogi & Co., Ltd.), 09 January, 1997 (09.01.1997), the whole document & EP 837052 A	1-11,13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 January, 2002 (04.01.02)	29 January, 2002 (29.01.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09435

Continuation of A.
31/343,31/40,31/404,31/407,A61P43/00,37/08,27/16,27/14,C07D333/40

Continuation of B.
31/343,31/40,31/404,31/407,C07D333/40

Form PCT/ISA/210 (extra sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/09435

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 12 relates to a method for treatment of the human body by therapy.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)